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ILEAL VALVE POUCH FOR URINARY TRACT DIVERSION

Preliminary Report of Eight Cases

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FOR many years surgeons have known that exstrophy of the bladder can be corrected by utilizing the rectum as a reservoir for the urine, and many types of surgical procedures have been advocated for transplanting the ureters into the rectosigmoid. In 1894, Maydl[1] recommended that the trigone of the bladder be implanted in the rectosigmoid, in the hope of minimizing the incidence of postoperative ureteral stenosis, stasis, and eventual pyelonephritis. However, until 1911, the operation was but infrequently advocated because the operative mortality and morbidity were extremely high. In 1911, Coffey[2] advocated the trough principle of implanting the ureters into the bowel; his technic (the Coffey I technic) has been widely used and has brought about a pronounced reduction in the operative mortality and morbidity.

Within the last few years, the Coffey I technic has been modified by performing a mucosa-to-mucosa anastomosis between the ureter and the rectosigmoid, in the hope of minimizing the incidence of stenosis at the site of implantation. Unfortunately, despite the meticulous care with which the anastomosis is made,

one potentially formidable complication may ensue, namely, ureteral obstruction. If the obstruction is slight and the patient has no renal infection, he may live a comparatively normal life for many years. Hyperchloremic acidosis, which may follow this surgical procedure, may be minimized or controlled by administering 10 per cent sodium citrate, the dosage being influenced by blood chemistry studies. But, only too often, as a review of published statistics reveals, ureteral obstruction and stasis cause pyelonephritis, and the patient subsequently dies from urosepsis and renal failure.

Recently the utilization of the isolated loop of ileum (Bricker[3]) as a reservoir for the urine has yielded gratifying results. Postoperatively hyperchloremic acidosis occurs less frequently, the incidence of ureteral obstruction appears to be reduced, and the incidence of pyelonephritis is minimal. The patient must wear a receptacle to collect the urine draining from the ileal pouch, or the ileal pouch may be catheterized at stated periods of time. This device causes very little discomfort and odor is avoided, yet many patients prefer if possible to avoid even this slight inconvenience.

The question, therefore, arose as to whether it would be feasible to combine the two operative procedures and eliminate the objectionable features of both: (1) To implant the ureters into an isolated ileal loop by a direct mucosa-to-mucosa technic, thereby minimizing the incidence of ureteral stenosis, hydroureter, hydronephrosis, and pyelonephritis with subsequent renal failure. (2) To implant the end of the isolated ileal loop into the rectosigmoid in order that the bowel may serve as a conduit for the urine. (3) To implant the free end of the ileum into the rectosigmoid in such a manner that stenosis will not ensue, and to provide a valvular mechanism for preventing reflux of gas and contents of the bowel into the isolated ileal loop.

It was proposed, therefore, that a Bricker's pouch[3] (uretero-ileostomy) be constructed so that the distal end of the pouch could be fashioned into an ileostomy and thrust into the sigmoid colon wherein accurate mucosa-to-mucosa anastomosis could be carried out, a combination of a one-way valve to prevent reflux with a known satisfactory method of urinary stream diversion. Experimental construction of such a pouch in the dog was successful in that barium could not be forced from the colon through the valve into the pouch.

This preliminary report is based on the early observation of eight patients each of whom had an isolated uretero-ileal pouch made after the method described by Bricker,[3] except that the ileostomy was placed *inside* the sigmoid colon to divert the urine internally and to act as a valve.

Technic

After examining the abdomen for other anomalies, we select an eight-inch segment of ileum and isolate it from the rest of the ileum about six inches proximal to the cecum. Next, the isolated segment is pulled posteriorly and the ileal continuity is restored above. The distal end of the isolated segment is freed

down into the depths of the mesentery to provide mobility, while the proximal end is freed to a lesser extent. A Babcock clamp is inserted into the distal end for a distance of two inches, the mucosa is gripped while the free end is pulled back, thus causing an intussusception for about two inches. The turned-over everted end of the ileum is sutured in position with five or six fine silk sutures so that a permanently everted ileostomy is constructed. Most of the fat of the everted ileostomy mesentery is trimmed so that it does not crowd or bulge the everted end. The entire isolated ileal segment is then turned counter-clockwise on its mesentery through 180 degrees so that the ileostomy rests on the left side of the pelvis while the other end rests on the right side. An incision is then made in the sigmoid colon three or four inches above the promontory of the sacrum, and the entire ileostomy is thrust in. Interrupted chromic catgut sutures are

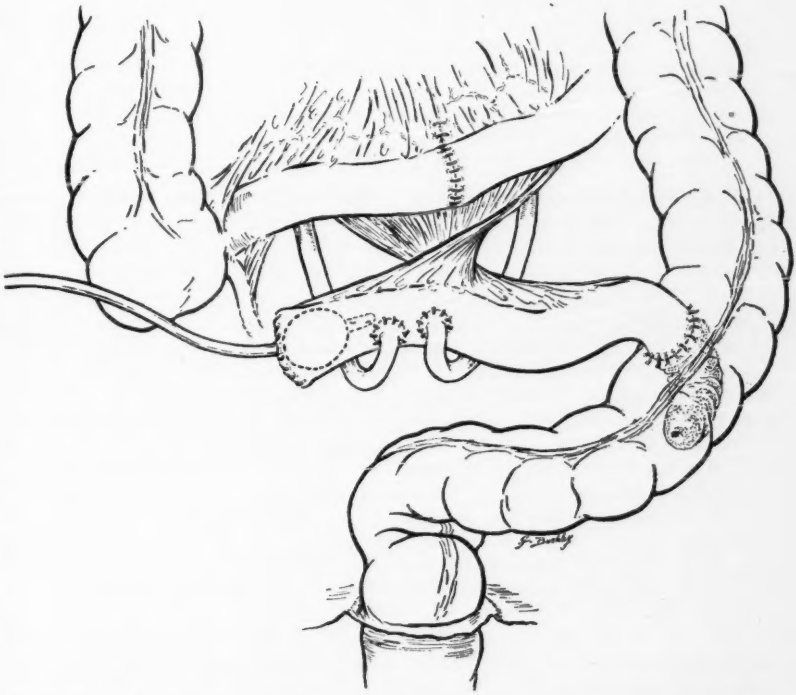

Fig. 1. Sketch showing the completed uretero-ileosigmoidostomy. The distal end of the valve pouch, with the turned-over everted end is in the sigmoid colon. The ureters are sutured to the ileal segment; the entire isolated ileal segment has been turned counter-clockwise through 180 degrees on its mesentery. The French No. 14 Foley catheter is in the antiperistaltic end of the pouch for temporary decompression.

placed between the turned-back end of the everted ileostomy and the wall of the colon around the colostomy, so that accurate mucosal approximation may be obtained. In addition, seromuscular sutures are placed.

The previously freed and divided ureters are now brought into the field in the region of the promontory of the sacrum, the left ureter having been drawn medially through the base of the mesentery of the sigmoid colon. Anastomosis between the ureters and the pouch (Fig. 1) is accomplished with a few fine chromic catgut sutures through the end of the ureter and through all layers of the ileum so that an accurate full-thickness and mucosa-to-mucosa anastomosis is obtained. Since the isolated ileal pouch and its various connections lie posterior and inferior to the rest of the small intestine, no particular obliteration of the various spaces seems to be necessary. A French No. 14 Foley catheter is inserted into the right side or antiperistaltic end of the pouch within an inch or two of the ureteral anastomoses, and the end of the pouch is closed with two layers of fine catgut. The catheter is drawn through the abdominal wall just above the inguinal ligament on the right side and is utilized as a retrograde (immediate) decompression apparatus for the pouch. The small intestine and the omentum are pulled down and the abdomen is closed.

Results

The valve pouch as described was constructed in the first patient on June 1, 1956; since then it has been constructed in eight patients. The indications and course for each were as follows.

(1) An infant boy, aged six months, with exstrophy of the bladder, had had bilateral ureterosigmoidal transplants followed by bilateral ureteral obstruction and pyelonephritis with intermittent uremia. A uretero-ileosigmoidostomy was performed and the convalescence was uncomplicated. Postoperative urograms and blood chemistry determinations showed little disturbance, with normal values for blood urea and a slight intermittent acidosis. The child remains well, although he has had two attacks of pyelonephritis, the last attack occurring eight months ago. The most recent urogram was made 12 months postoperatively and the degree of hydronephrosis and hydroureter was the same as that noted prior to surgery; there has been good renal drainage.

(2) A girl at the age of two years, because of exstrophy of the bladder, had the right and left ureters transplanted into the sigmoid colon. Two years later a valve pouch was constructed because of progressive and marked left hydronephrosis and decreased function in the right kidney with hydronephrosis. The hospital course and postoperative period was uneventful; so far (three-month follow-up) there has been no evidence of pyelonephritis.

(3) An infant boy, aged 9 months, in March 1957, because of exstrophy of the bladder and a rather marked prolapse of the rectum, underwent uretero-ileosigmoidostomy and construction of a valve pouch rather than transplantation of the ureters directly into the sigmoid colon. During the postoperative period a low-grade fever developed and it was thought that a mild urinary tract infection was in progress. However, this was easily controlled with antibiotics. A urogram was normal one month following the surgical procedure. Blood chemistry evaluations have revealed normal blood CO_2 content and urea concentration. Further studies are planned.

(4) A woman, aged 18 years, was observed with exstrophy of the bladder bilateral hydroureters, hydronephrosis, and renal failure. On September 22, 1947, at the age of seven years, she underwent bilateral cutaneous ureterostomy. In June 1957, a valve pouch was constructed so that she could be socially rehabilitated. One month following surgery, severe pyelonephritis developed and was treated effectively with antibiotic drugs; and the urogram revealed a moderate hydronephrosis and hydroureter but to a lesser degree. Blood chemistry studies revealed normal CO_2 and urea values.

(5) A boy, aged five years, had exstrophy of the bladder. A valve pouch was constructed primarily rather than ileosigmoidal transplants. The postoperative course was uneventful. Blood values for urea, CO_2, chlorides, and sodium were normal. Follow-up roentgen studies are planned.

(6) An infant boy, aged 16 months, had exstrophy of the bladder. Two attempts were made to reconstruct the bladder; however, both times the bladder extruded through the closure. A valve pouch was constructed rather than ileosigmoidal transplants. A minimal postoperative fever was interpreted as being caused by a mild infection of the urinary tract and responded to antibiotic drugs. The child remains well after two months and has gained weight. Follow-up urogram and blood chemistry evaluations are planned.

(7) A boy, aged 13 years, had exstrophy of the bladder. Two previous attempts elsewhere to reconstruct the bladder failed. A valve pouch was constructed and the postoperative course was uneventful. Postoperative blood CO_2, urea, sodium, and chloride values were normal. The urogram made on the tenth postoperative day revealed moderate hydronephrosis and hydroureter. Further postoperative studies are planned.

(8) An infant boy, aged 14 months, had bilateral ureterosigmoidal anastomosis performed at the age of eight months, resulting in ureteral obstruction with nonvisualization of the left and right hydroureter, hydronephrosis and pyelonephritis, and intermittent uremia with hypertension. Bilateral cutaneous ureterostomy was performed as a preliminary procedure and two weeks later a valve pouch was constructed. Blood urea values dropped rapidly from 60 to 16 mg. per 100 ml. and by the tenth day the blood pressure was normal. The blood chemistry values for urea, CO_2, and chlorides have remained normal. There has been no evidence of pyelonephritis. Follow-up studies are planned.

Discussion

Because of the short follow-up time no definite conclusions can be reached as to whether this type of urinary tract diversion will continue to function satisfactorily. Except for the first patient in whom the pouch was constructed, the follow-up period with blood chemistry studies and roentgen examinations of the urinary tract is insufficient or of too short a duration. However, the 15-month course of the first patient is encouraging.

Mechanically, the pouch seems to be effective. Gas or feces have not been observed to reflux through the catheter placed in the pouch at the time of surgery, and the urine is ejected completely into the sigmoid colon through the intrasigmoid ileostomy. Colon roentgenograms taken after barium enema and rectal air insufflation have failed to reveal any reflux into the pouch. Cineradiographic films show a competent valve.

Conclusions

An ileal valve pouch for internal diversion of the urinary tract through a uretero-ileosigmoidostomy has been constructed in eight patients. Conclusions as to its ultimate effectiveness cannot be stated at this time, but to date the end-in-side ileosigmoidal anastomosis has prevented gross reflux of gas and feces into the isolated ileal segment. Roentgen studies of the urinary tract, together with frequent blood chemistry evaluations have been made in one half of the cases and have indicated good function. In the event of late complications or failure of the pouch to function as proposed, the distal end may be retrieved from the sigmoid colon and brought out on the surface of the skin as an ileostomy, thus converting to the known Bricker's[3] pouch.

References

1. Maydl, K.: Ueber die Radikaltherapie der Blasenektopie. Wien. med. Wchnschr. **44**: 1113, 1169, 1209, 1256, 1297, 1894.

2. Coffey, R. C.: Physiologic implantation of severed ureter or common bile-duct into intestine. J.A.M.A. **61**: 397-403, 1911.

3. Bricker, E. M.: Substitution for urinary bladder by use of isolated ileal segments. S. Clin. North America **36**: 1117-1130, Aug. 1956.

METABOLIC ACIDOSIS AND ITS CORRECTION IN PATIENTS UNDERGOING OPEN-HEART OPERATION

*Experimental Basis and Clinical Results**

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THE occurrence of metabolic acidosis in patients undergoing open-heart operation has been recognized by Lillehei and his associates.[1] According to our observations, the most significant changes in blood pH occur not during, or immediately after operation, but about three hours postoperatively. As long as the patient is under anesthesia and his respiration is "helped" by the anesthetist, an excess of CO_2 is blown off and the pH does not fall significantly. While the patient's circulation is being maintained by the heart-lung machine, the removal of CO_2 via the oxygenator also helps to keep the pH within normal limits. However, three or more hours after completion of the operation the blood pH occasionally falls to a level that is incompatible with life. Whatever the underlying cause, the mechanism of death in some cases seems to be an acidosis leading to respiratory failure followed by cardiac arrest.

It has been suggested that these unfavorable acid-base imbalances are caused by damage to the blood itself by the pump-oxygenator during the period of bypass. This hypothesis, however, is not supported by the data in this paper. Our experimental results demonstrate that the blood pH and the CO_2 content can be lowered simply by reducing the cardiac output. Our clinical results show that the occurrence of reduced blood pH and CO_2 content in patients treated with a heart-lung machine is correlated with corresponding periods of hypotension before, during, or after the period of bypass. Furthermore, unfavorable changes in blood pH and CO_2 content are known to occur even in patients who have had no extracorporeal circulation with a heart-lung machine. Finally, we have been able to prevent or reduce acidosis by administering sodium bicarbonate intravenously as a continuous drip during the postoperative course.

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MATERIAL AND METHODS

The clinical results are based upon 35 consecutive patients who underwent open-heart operation at the Cleveland Clinic* while aided by a heart-lung machine. The types of artificial heart-lung used were the membrane oxygenator,[2] the Melrose oxygenator,[3] the Björk oxygenator,[4] and the modification of the Björk oxygenator as described by Kay and associates.[5]

The blood samples for the pH and CO_2 determinations were drawn into a sterile syringe containing light mineral oil, heparin, and an aqueous solution of sodium fluoride. In patients the samples were taken from high in the inferior vena cava through an indwelling polyethylene catheter which has the advantage that the patients need not be disturbed. We realize that the changes in the pH and CO_2 content of central venous blood are not identical to those of the arterial blood but they run parallel. The pH of arterial blood may be expected to be a little higher, whereas the CO_2 content is somewhat lower than for caval blood.

In the experimental study mongrel dogs weighing approximately 10 kilograms each were used. Blood samples were taken from the femoral artery through an indwelling catheter.

Blood pH was determined with the Cambridge Research Model pH meter** using a micro-glass electrode (0.4-ml. capacity). Determinations were made either at room temperature and corrected to 38 degrees C. by means of Rosenthal's correction formula[6] or were made at 38 degrees C. with a water-jacketed micro-glass electrode assembly maintained at that temperature. Values obtained in either way were within the limits set by the over-all inherent error of the instrument.

Determinations of CO_2 content of blood plasma were made with the manometric Van Slyke apparatus, and were reported as millimols per liter. The pCO_2 values were read from the chart of Van Slyke and Sendroy.[7]

In patients in whom a low pH was expected, a standard procedure was followed: 4.5 mEq. of sodium bicarbonate (commercially available† as 50-cc. ampuls containing 44.6 mEq.) per kilogram of body weight was diluted with a double volume of 5 per cent fructose in water and started as a slow intravenous drip to be injected during the first six hours following operation. The pH was determined at the third and at the sixth hour postoperatively and if it was found to be normal or corrected, infusion was discontinued. However, if the pH and CO_2 content still were low after six hours and after completion of this dose, a second similar dose was started, to be injected during the next 12 hours.

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EXPERIMENTAL WORK

Experiments with Partial Ligation of the Venae Cavae

A dog was anesthetized with pentobarbital (Nembutal) sodium, was put on a respirator and the chest was opened.* Ligatures were placed around the venae cavae which gradually were occluded until the mean arterial pressure in the femoral artery, as measured with a Tycos manometer, was lowered to 40 mm. Hg. Figure 1 shows the course of events in one such experiment. The values of

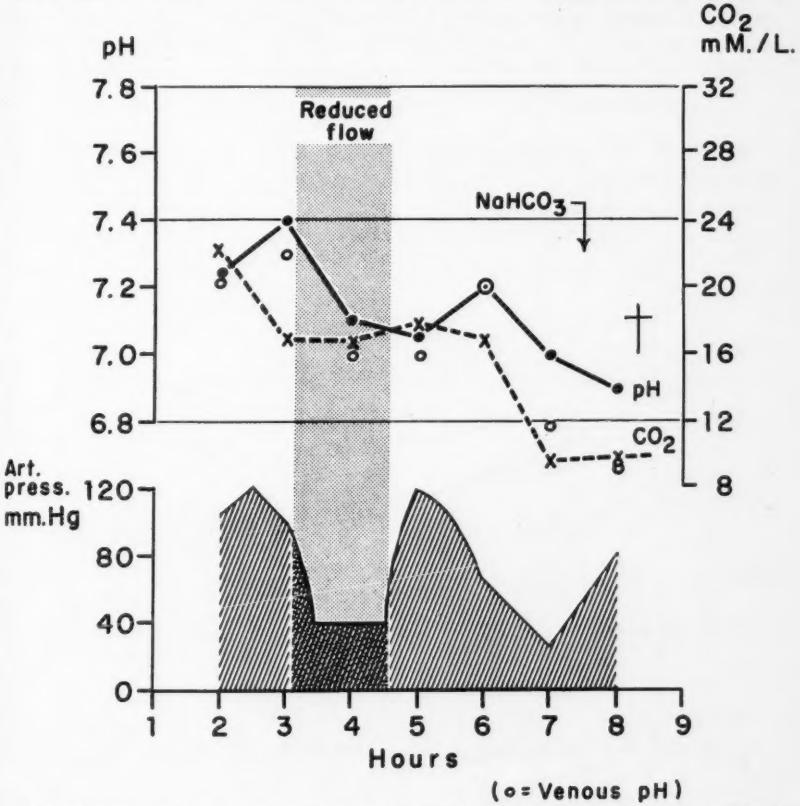

Fig. 1. Chart showing the course in a dog in which partial ligation of the venae cavae reduced the arterial pressure to 40 mm. Hg. Fall in pH of the arterial blood (black dots and solid line) parallels the more severe fall in central venous pH (white dots). Note the progressive decrease in CO_2 content, expressed in millimols per liter, until $NaHCO_3$ was administered. (This experiment was done by Edward Miller, M.D.)

Preliminary experiments in our laboratory were performed by Edward Miller, M.D., formerly a Special Fellow in the Division of Research.

the pH of the blood in the inferior vena cava paralleled but generally were lower than those of the arterial pH. The CO_2 content fell from 22 to 16 millimols before partial occlusion of the venae cavae. This was due to overventilation by the respirator. It resulted in a correction of the pH at that time. The pH and CO_2 content fell during the period of reduced cardiac output but a more severe fall in CO_2 content and pH took place two hours later. This experiment, together with four other experiments not reported, demonstrates that changes in pH and CO_2 content, which are similar to those in patients treated with the artificial heart-lung, can be reproduced in the laboratory simply by limiting the cardiac output by partially ligating the venae cavae.

Experiments with Balloons Inflated in Venae Cavae

In order both to avoid the trauma of opening the chest and to define the cause of the acidosis more clearly, the circulation was reduced by inflating balloons in the venae cavae. Catheters with small balloons at their tips were inserted from peripheral veins into the venae cavae of anesthetized dogs. The

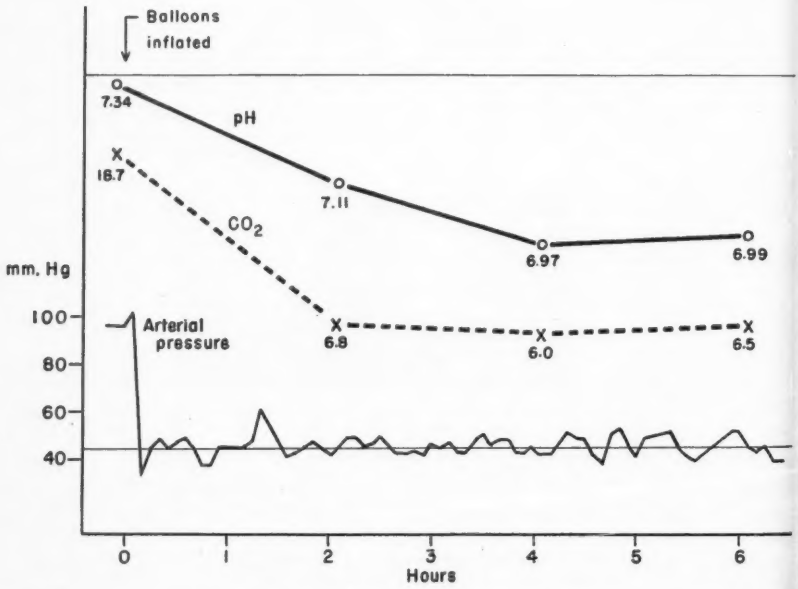

Fig. 2. Graph showing course in a dog in which balloons were placed in the venae cavae and were inflated until the mean arterial pressure was reduced to 45 mm. Hg. Note the remarkable decrease both in pH and CO_2 content (millimols per liter) of arterial blood.

balloons then were more or less inflated so that the mean arterial blood pressure could be maintained at the predetermined low level of 45 mm. Hg. Four such experiments were performed and all of them showed the same phenomenon. Figure 2 shows the course in one such experiment. The pH fell to 6.97 and the CO_2 content fell from 18.7 to 6.0 millimols per liter.

In a similar experiment (Fig. 3) the pH fell to 6.86 and the CO_2 content to 6.0. Sodium bicarbonate was given intravenously in the usual dose. The pH started to rise and the CO_2 content remained virtually the same. Thus, six hours after the onset of the reduction of cardiac output the pH had been corrected to 7.28 but the CO_2 content was down to 6.3 millimols per liter. This demonstrates that although the acidosis was partly corrected, the administered bicarbonate was eliminated.

The pCO_2 calculated in the above-mentioned experiments is not elevated and indicates that the acidosis was not due to respiratory retention of CO_2 but must have been due to the accumulation of metabolic acids.

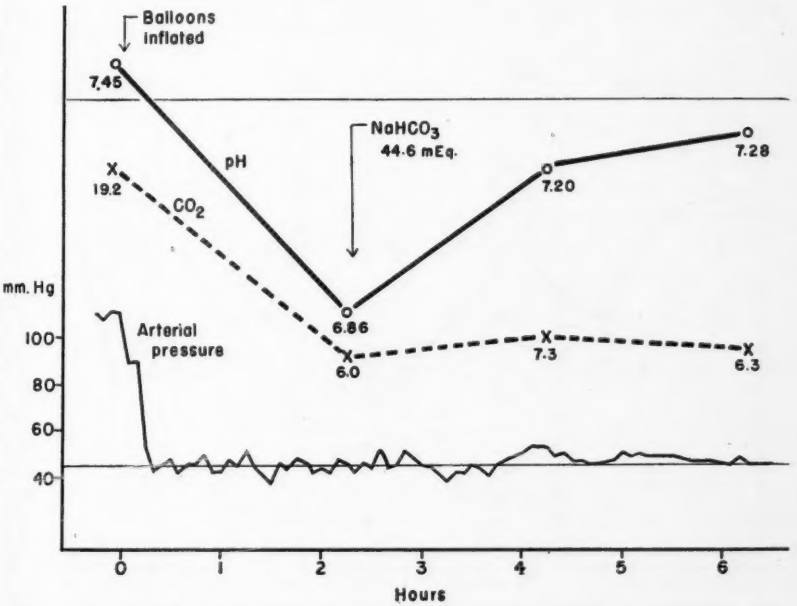

Fig. 3. Graph showing course in a dog (similar experiment as that represented in Fig. 2) in which $NaHCO_3$ given intravenously increased the pH although the CO_2 content remained low.

CLINICAL EVIDENCE

All patients had less than normal circulation (artificial cardiac output) during bypass but "hypotension" was used as evidence of grossly inadequate circulation. "Hypotension" was considered to be present if the mean arterial blood pressure was less than 50 mm. Hg during the time of extracorporeal maintenance of the circulation, or if in the prerun or postrun phases the mean arterial blood pressure was less than 60 mm. Hg. The duration of low blood pressure should be longer than two minutes in order to be regarded as hypotension.

The data of 35 consecutive patients treated with heart-lung machines conformed to the well-known fact that younger children are more apt to develop acidosis than adults. Figure 4 shows the scattergraph of the pH of 12 patients in whom no attempts were made to correct acidosis with sodium bicarbonate. It is evident that the lowest pH values, averaged at 7.25, may be found not during or immediately after the bypass but three hours later. Because of overventilation by the machine and the anesthetist, the CO_2 content for this group was lowest immediately after the bypass and returned to an average of 21 millimols three hours after the run on the heart-lung machine.

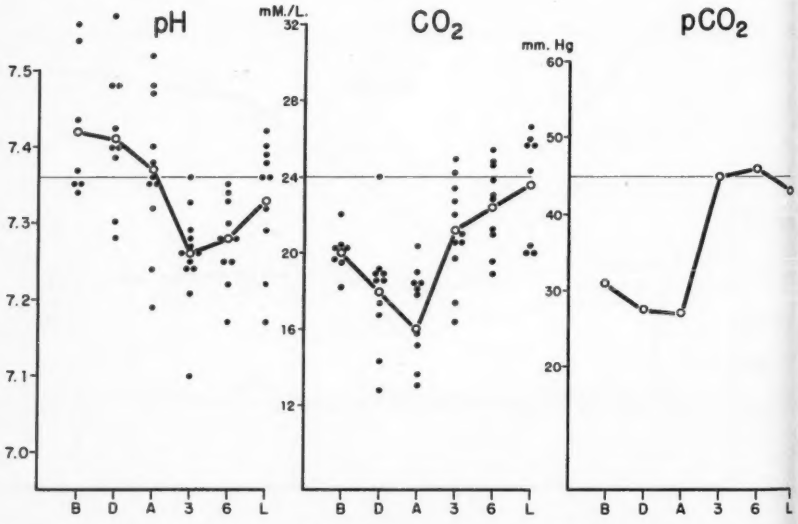

Fig. 4. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines and not given $NaHCO_3$. At the abscissas: **B,** before bypass; **D,** during bypass; **A, 3, 6,** immediately, three hours, six hours, respectively, after completion of bypass; **L,** later. A slight degree of acidosis is present, which is metabolic as the pCO_2 is low or normal.

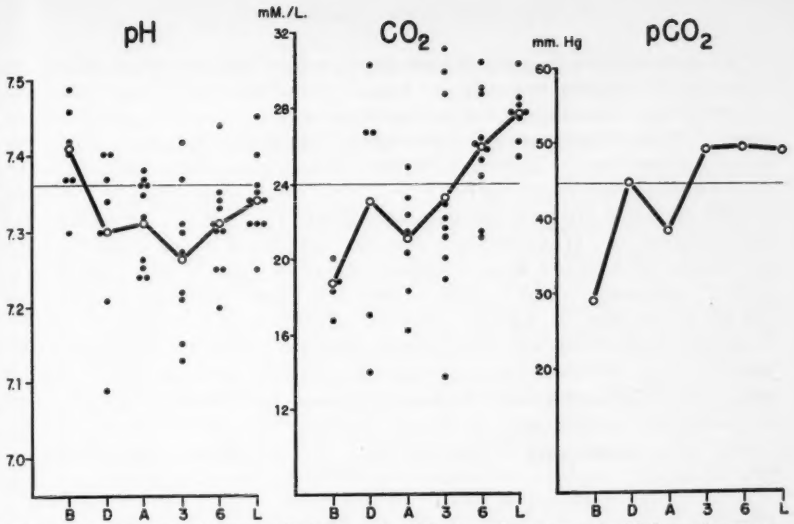

Fig. 5. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines, who were given $NaHCO_3$, but who had no hypotension as defined for this study. The $NaHCO_3$ was given because acidosis was expected. Nevertheless, the lowering of the pH three hours after completion of surgery still is evident.

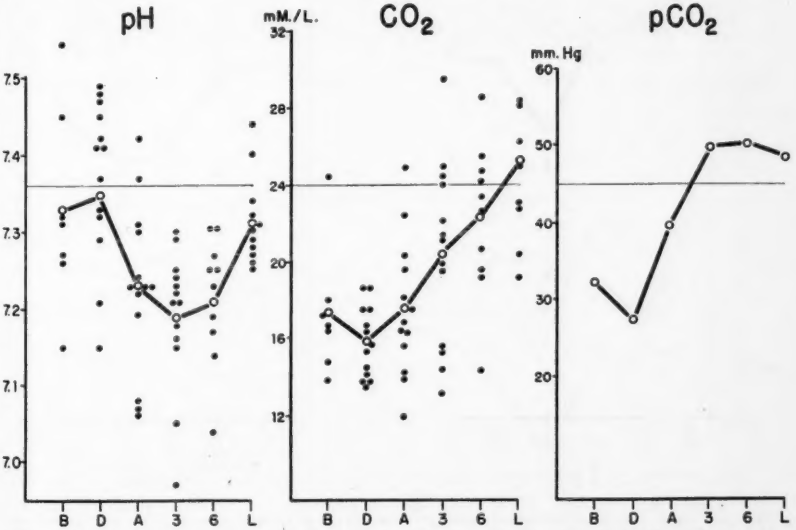

Fig. 6. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines, who were given $NaHCO_3$, and who had hypotension as defined for this study. Notwithstanding the administration of $NaHCO_3$, acidosis is more marked than in the non-hypotensive patients represented in Figure 5.

In the remaining 23 patients more severe acidosis was expected and sodium bicarbonate was given to correct it on an empirical basis. The 23 patients were classified into two subgroups: those in whom no "hypotension" occurred, and those in whom "hypotension" as previously defined occurred. According to our criteria there were 13 patients with and 10 patients without "hypotension." As the distinction between the two groups is not sharp, overlapping in the results is to be expected. Figure 5 shows a scattergraph of the pH of patients who had no "hypotension." It may be seen that the average pH in this group does not fall below 7.26. Figure 6 shows a scattergraph of the patients who, according to their "hypotension," had a more severely decreased circulation; the average pH fell to less than 7.2. In both subgroups, the lowest point of the pH was not during, or immediately after, but at least three hours after the bypass. The CO_2 determinations for these two subgroups show that the average CO_2 content in the group with "hypotension" is about 4 millimols less than in the group with no

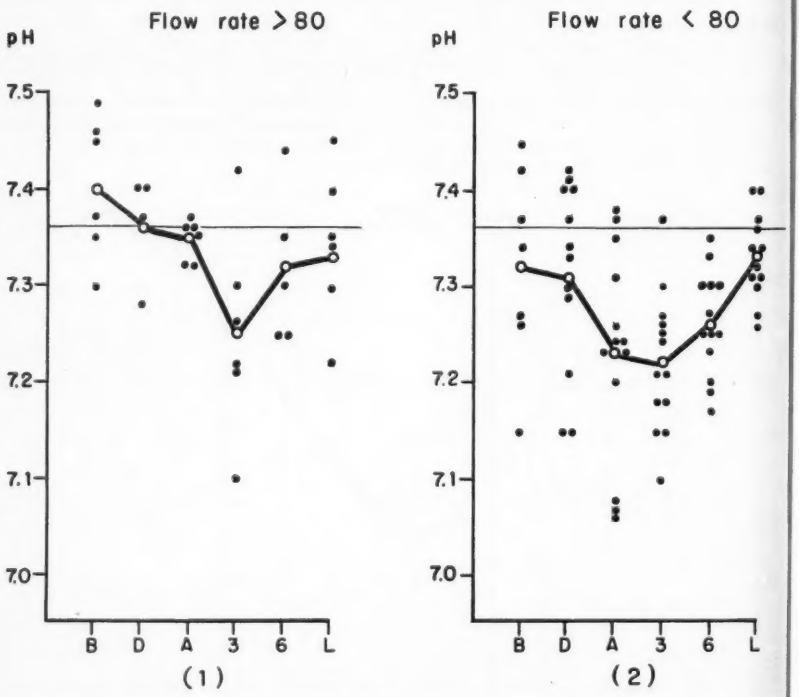

Fig. 7. Graph showing the correlation between blood pH changes and flow rate during the bypass circulation. (1) pH changes when the flow rate was greater than 80 ml. per kilogram per minute. (2) pH changes when the flow rate was less than 80 ml. per kilogram per minute. The average pH is lower and stays low longer. (Only patients weighing from 10 to 20 kg. are represented in this graph.)

"hypotension." These data support our thesis that the metabolic acidosis occurring after open-heart operation may be due to the decreased circulation, as the acidosis is more severe when the circulation is so reduced as to cause "hypotension." Finally, in all of these groups the pCO_2 was not elevated (Figs. 4, 5, 6) so that the acidosis is considered to be metabolic rather than respiratory.

For a group of 19 patients weighing from 10 to 20 kilograms each, the flow rate during the bypass was correlated with the degree and duration of the acidosis (Fig. 7). In six cases with a bypass flow rate greater than 80 ml. per kilogram per minute, the average pH six hours after bypass was 7.32. In 13 cases with flow rates less than 80 ml. per kilogram per minute it was 7.26. The changes probably would be more significant had they not been corrected by sodium bicarbonate.

If the low pH and low CO_2 content occurring after periods of bypass are caused by the decreased circulation, then it is a phenomenon that could be expected to occur in some patients not subjected to the extracorporeal circulation; and perhaps the reason why so little attention has been paid to it is that such changes have not been looked for at the proper time. Our experience supports this contention.

A large interatrial septal defect was closed in a patient during maintenance of the artificial circulation with the heart-lung machine for 29 minutes. The run was uneventful and the mean blood pressure never fell below 60 mm. Hg. The blood pressure was 80 mm. Hg before, and from 70 to 120 mm. Hg after the run. The pH, which had been too high because of overventilation, was 7.3

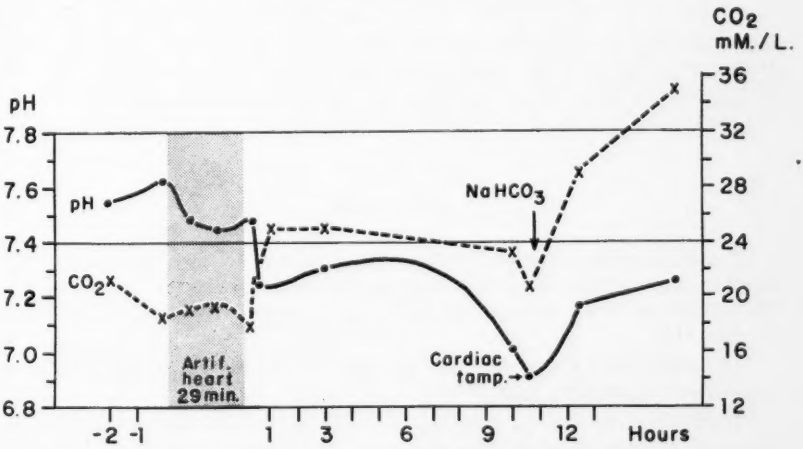

Fig. 8. Graph showing the blood pH and CO_2 changes and the effect of $NaHCO_3$ in a patient in whom cardiac tamponade occurred after closure of an interatrial septal defect. Although the open-heart operation with the aid of an artificial heart-lung caused little change in the pH, the period of reduced circulation owing to cardiac tamponade reduced it to 6.9.

three hours after the run. That night the patient developed cardiac tamponade and had a period of extremely low blood pressure followed by cardiac arrest, but was revived by means of cardiac massage. The pH fell to 6.9, intravenous administration of the usual dose of sodium bicarbonate was started, and the blood pressure was restored after release of the cardiac tamponade. As may be seen from Figure 8 the pH was rapidly corrected to 7.2 and later to 7.3. The patient recovered.

A patent ductus of the "window type" with partial shunt reversal was closed with considerable difficulty in a boy 15 years of age; a heart-lung machine was not used. During operation he had several periods of severe hypotension because of technical difficulties. His initial recovery was satisfactory; however, on the following day he became cyanotic and lethargic without obvious cause. A pH determination revealed a pH of 7.0. The patient was given sodium bicarbonate by mouth, and his clinical condition improved within a half hour.

CONCLUSIONS

Metabolic acidosis occurring after open-heart operation is manifested not during, or immediately after, but three or more hours after the completion of operation. This metabolic acidosis most likely is due to a period of decreased circulation, as it was correlated with the period of hypotension, and as it was experimentally produced by restricting the cardiac output. Severe metabolic acidosis was prevented or corrected by slow intravenous administration of sodium bicarbonate during the postoperative course.

Severe metabolic acidosis sometimes leading to respiratory arrest followed by cardiac arrest and death also occurs in surgical patients who have not been treated with the heart-lung machine but who have been subjected to a period of decreased circulation. It should be looked for more frequently, since the acidosis is a condition that can be controlled or corrected.

SUMMARY

Experimentally, metabolic acidosis was produced in dogs by reducing the cardiac output either by partially ligating the venae cavae or by filling catheter tip balloons until the systemic arterial blood pressure was maintained at about 45 mm. Hg.

Clinically, the CO_2 content and pH were studied in 35 consecutive patients treated with heart-lung machines.

$NaHCO_3$, 4.5 mEq. per kilogram, was administered within the course of six hours in patients in whom a severe drop in pH was expected. The infusion was discontinued whenever the downward trend of the pH was controlled.

A drop in pH was evident three or six hours after operation, not during or immediately after the bypass.

The severity of this drop could be correlated with the occurrence of hypotension before, during, or after the bypass.

ACKNOWLEDGMENT

We are especially appreciative of the excellent assistance of our technicians: Mr. Thomas O'Mara, Mr. Robert Placko, Mr. Janis Eglajs, and Miss Rose Litturi.

References

1. DeWall, R. A.; Warden, H. E.; Gott, V. L.; Read, R. C.; Varco, R. L., and Lillehei, C. W.: Total body perfusion for open cardiotomy utilizing bubble oxygenator; physiologic responses in man. J. Thoracic Surg. **32**: 591-603, Nov. 1956.
2. Kolff, W. J.; Effler, D. B.; Groves, L. K.; Peereboom, G., and Moraca, P. P.: Disposable membrane oxygenator (heart-lung machine) and its use in experimental surgery. Cleveland Clin. Quart. **23**: 69-97, April 1956.
3. Melrose, D. G.: Heart-lung machine for use in man. J. Physiol. **127**: 51-3P., March 28, 1955.
4. Kolff, W. J.; Effler, D. B.; Groves, L. K., and Moraca, P. P.: Elective cardiac arrest with potassium citrate during open-heart operations. J.A.M.A. **164**: 1653-1660, Aug. 10, 1957.
5. Kay, E. B.; Zimmerman, H. A.; Berne, R. M.; Hirose, Y.; Jones, R. D., and Cross, F. S.: Certain clinical aspects of use of pump oxygenator. J.A.M.A. **162**: 639-641, Oct. 13, 1956.
6. Rosenthal, T. B.: Effect of temperature on pH of blood and plasma in vitro. J. Biol. Chem. **173**: 25-30, March 1948.
7. Van Slyke, D. D., and Sendroy, J., Jr.: Studies of gas and electrolyte equilibria in blood; line charts for graphic calculations by Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. Biol. Chem. **79**: 781-798, Oct. 1928.

POSTOPERATIVE CARE OF THE OPEN-CARDIOTOMY PATIENT

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OPEN-CARDIOTOMY patients require a postoperative program that is individualized and meticulously supervised. There are no rules that can serve as a fixed guide for proper care. Experience in 103 operations, in 86 of which we performed elective cardiac arrest with potassium citrate,[1,2] has established for us a set of procedures useful in the postoperative care. It is the intent of this paper to elaborate upon these basic observations. It is not necessary to review the general care of patients recovering from thoracic surgical procedures; our interest is confined at present to patients who have undergone open cardiotomy. The details of this postoperative program are of particular import in the care of children; adults do not require such precise attention, as their larger body mass makes small variations relatively less important.

Immediately Postoperative Care

The changes in patients during the hours immediately after open cardiotomy are sufficiently rapid and severe that it is mandatory to have a qualified team in constant attendance. This is best accomplished with a special-care unit designed and equipped exclusively for these patients. The basic team should include a resident physician well trained in thoracic surgery, and experienced nurses who are particularly interested in the field of cardiac surgery. A fortunate selection of capable personnel may be rewarded by a self-perpetuating system as the service demands grow. A detailed description of the equipment will not be given here; suffice it to say that the usual implements of the recovery room are basic and must be augmented by such specialized equipment as Croupettes, intermittent positive-pressure-demand valves (such as the Bennett device), a large-screen monitor for the electrocardiogram, and specialized emergency pharmaceuticals. Equally as important is the need for prompt and accurate laboratory support that will include the radiologic services, blood bank facilities, and the all-important clinical laboratory. Without this extensive and expensive basic support, the mortality rate of open-heart operations will soar.

Although there is still much to be learned about the care of these patients, we have tried to consolidate our observations under three headings that we consider to represent the basic guiding principles of management.

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1. Establishment of minimal metabolism to lessen cardiac work. During the first 24 postoperative hours the traumatized myocardium has a better opportunity to perform its functions if it is spared sudden or excessive demands. In patients with severe pulmonary hypertension, avoidance of effort may make the difference between survival and death. It has been our misfortune to have two patients die while they were being needlessly disturbed. For this reason we temper our zeal for examination by avoiding any act that imposes strain or emotional stress on the patient. Excess activity is prevented by giving the patient sedatives for restlessness. In children, aspirin given rectally frequently is effective; otherwise, we use meperidine (Demerol) hydrochloride or small doses of a barbiturate. The frequent occurrence of hyperpyrexia in the early postoperative hours necessitates frequent recordings of the body temperature. It is well to note that electrical devices may become unreliable and body temperature should be repeatedly checked with a mercury thermometer. Aspirin given rectally and the use of a cool oxygen tent generally suffice to prevent an undue rise in temperature. However, if fever persists, alcohol sponging or ice packs are employed. In our experience, the ice-water mattress has proven unsatisfactory. Hypopyrexia in the patient with a small body mass may be just as serious a problem, particularly in the immediately postoperative period. It is our impression that hypopyrexia in part causes or aggravates cyanosis and metabolic acidosis. We make every effort to raise the body temperature of a cold patient by using hot-water bottles or warm blankets.

2. Establishment and maintenance of cardiovascular stability. To establish a base line, careful preoperative and postoperative weighings of children are performed. A close balance is established between the amount of blood lost and the amount transfused during operation. This blood replacement must be consistent with optimal filling of the cardiovascular system, as evaluated while the chest is open. The balance between blood lost and blood replaced will be a direct guide to additional transfusions during the postoperative course. The clinical evaluation of the cardiovascular system at operation, when the heart and the great vessels can be seen and palpated, is a reliable guide. It is our practice to use high saphenous vein cannulations on all of our patients. A constant recording of the central venous pressure is then obtained and is a helpful guide to the status of the blood volume and cardiac dynamics. A corollary to establishing a careful base line is to establish careful postoperative control. Hemoglobin and hematocrit determinations are performed immediately after operation. Using chest suction of from 10 to 15 cm. of water and bilateral trap bottles, the amount of bleeding from each side of the chest is carefully recorded and blood replacement made as indicated. This method is of particular value in children, in whom even small blood loss is important. Additional adjuncts include frequent recordings of the blood pressure, pulse, and a visual electrocardiographic recording for the first few hours. Excessive postoperative bleeding in the open-cardiotomy patient is a worrisome complication and of far greater significance than when encountered in standard thoracotomy procedures. This is in part due to the extensive operation itself, but also to acquired tendencies

to bleed which may be induced by the heparin, the pump-oxygenator, or the multiple transfusions. Meticulous hemostasis is a surgical necessity. When unexpected bleeding occurs, clotting time should be determined. The possibility of "heparin rebound"[3] should be considered and additional protamine may be required. Excessive bleeding in spite of an adequate clotting time must be regarded as a technical problem and prompt reoperation must be considered.

3. Establishment and maintenance of an optimal respiratory function. Adequate oxygenation and prevention of significant laryngeal edema have been accomplished by the use of cold humidified oxygen administered by the Croupette for children and the Melco nebulizer for adolescents and adults. Tracheotomy is useful for those patients who develop bronchorrhea or pulmonary edema. Prophylactic tracheotomy facilitates tracheal toilet; it also permits the use of intermittent positive pressure to supplement the natural pulmonary exchange. It is particularly helpful in those patients who manifest severe pulmonary hypertension prior to operation; such patients are prone to "wet lungs" during the immediately postoperative period. We have intravenously administered a constant drip of aminophylline for the first 12 to 24 hours in an attempt to decrease the pulmonary hypertension and thereby lessen the load on the traumatized right side of the heart; however, we are not convinced that this procedure is beneficial.

Incisional pain during the first 24 hours may severely limit pulmonary excursion, particularly in older children and adults. Intercostal nerve blocks, repeated as needed, will add to the patient's comfort and improve respiratory exchange. Occasionally, a positive-pressure respirator of the demand type may be effective in improving an otherwise inadequate ventilation. A portable anteroposterior chest roentgenogram is taken from four to six hours after operation to evaluate pulmonary expansion and thoracic drainage.

Gastric distention is a common and unpleasant complication. In all patients, a gastric tube is left in place for from 24 to 36 hours, after which time oral feedings are started.

Fluid and electrolyte imbalances have not been a major problem. We routinely use 5 per cent dextrose or fructose in water as the intravenous solution. Saline solution should be avoided. Unless these patients have polycythemia, they are kept slightly underhydrated. In calculating the fluid requirements, it must be remembered that the amount of insensible water loss is decreased while the patient is breathing highly humidified air.

Surgery with extracorporeal circulation usually is associated with some degree of metabolic acidosis. The effect of the procedure on serum carbon dioxide content depends in part on the type of oxygenator employed, as each oxygenator varies in the amount of carbon dioxide it releases during the oxygenation process. When more carbon dioxide is released than normally would be released through the alveolar membrane, a partial balance is established between respiratory alkalosis and metabolic acidosis. Thus, the changes in the pH of the serum vary with the type of oxygenator. As a general rule, unexpected cyanosis suggests the presence of significant acidosis, and prompt pH determina-

tions of the serum are indicated. If the determinations confirm the clinical suspicion, a sodium bicarbonate infusion is given.*

Antibiotics are included in routine care. It is our practice to begin the course of antibiotics two days prior to operation and to continue for about one week. The usual antibiotic therapy is a combination of penicillin and streptomycin.

If the patient's condition appears to be stabilized on the evening of the day of operation, the constant recording of temperature and the electrocardiographic tracing may be discontinued. If bleeding is no longer a problem, the chest suction is discontinued and the thoracotomy tubes are then connected to waterseal drainage.

Later Postoperative Care

After the first day postoperative care becomes an individual matter that depends entirely upon the patient's progress. The need for oxygen is extremely variable and in most cases its administration will be reduced or terminated within 24 hours. Cold steam, however, may be required for an indefinite period in those patients who demonstrate pulmonary vascular changes. An upright chest roentgenogram is desirable on the first postoperative day if the patient's condition permits. There is little doubt that a good roentgenogram is of greater value than the most skilled physical examination. Diet is another individual matter and will be influenced by the presence and persistence of gastric dilatation. An effort is made to start clear liquids by mouth within 24 hours. By from 36 to 48 hours postoperatively, the thoracotomy tubes usually have stopped functioning and are removed. For a child we do not use a low-salt diet unless there is evidence of cardiac failure or unless such a diet had been used prior to operation.

Digitalis is used only if it had been given preoperatively or if there is evidence of cardiac failure. If the patient is progressing satisfactorily, movement in bed is encouraged on the second postoperative day, and on the third day after operation ambulation gradually is begun. Chest roentgenograms and electrocardiograms are taken as indicated by the patient's clinical course. A complete electrocardiogram and chest roentgenograms for cardiac size are taken before the patient is discharged from the hospital. This discharge occurs in the uncomplicated cases about two weeks after operation.

Complications

Open cardiotomy is associated with many postoperative complications, some of which already have been mentioned but merit repetition. A temperature running as high as 104 degrees Fahrenheit without known specific etiology

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*Sodium bicarbonate, in an amount equal to 4.5 milliequivalents per liter per kilogram of the patient's weight, administered intravenously for a period of two to six hours has proved satisfactory.

is common. This usually is self-limited and subsides within five days; if the fever is severe, aspirin can be given in regular doses for its control.

As stated before, metabolic acidosis is a common problem and usually occurs in the immediately postoperative period. The exact cause of this acidosis is not entirely understood but inadequate perfusion, prolonged hypotension, and inadequate ventilation are known contributory factors. Metabolic acidosis will be reflected by a drop in the pH of the serum, and we believe that the laboratory facility for this determination is mandatory. In most cases, the pH will rise and the patient's condition will improve after the administration of sodium bicarbonate. Persistent acidosis is an ominous finding and implies irreversible damage, the exact nature of which is poorly understood.

A combination of fever, cough, chest pain, and roentgen evidence of a bilateral patchy pneumonitis occurs in a number of cases. This syndrome closely resembles the postmitral commissurotomy syndrome. This also appears to be a self-limited disease, but lasts from one to three weeks. Therapy consists of the usual doses of aspirin or, if not controlled by this drug, steroids are given in doses sufficient to overcome the signs and symptoms.

Acute and subacute bacterial endocarditis occurring in either traumatized valve leaflets or intracardiac suture lines is a grave complication. Treatment is the same as for any other case of subacute bacterial endocarditis, that is, supportive measures with massive doses of bactericidal antibiotics. *Aerobacter aerogenes* was isolated from our only proven case.

Chylothorax occurring from eight to ten days postoperatively complicated two of our cases. It is our belief that the thoracic duct, or a major radical, was damaged inadvertently during the dissections for cannulation of the subclavian artery. The insertion of a water-seal drainage tube, as reported by one of us (D. B. E.),[4] has been effective treatment.

Cardiac failure may result as a consequence of altering the cardiac dynamics during the open-heart procedure. The common causes of cardiac failure are: (1) severe pulmonary hypertension with fixed resistance, (2) residual outflow obstruction of the right ventricle, and (3) uncorrected mitral or tricuspid insufficiency. This complication is manifested by elevation of the venous pressure, enlargement of the liver and, in the acute phase, air hunger and poor color. Obstruction to the right ventricular outflow tract, which is not completely relieved at the time of operation or perhaps is produced by the surgical procedure, should be suspected when there is a significant gradient between the ventricular and the pulmonary artery pressures after operation.

Heart block of varying degrees is not at all unusual; however, complete atrioventricular dissociation has occurred only nine times in our series, and it has been permanent in only three patients. The action of isopropylarterenol (Isuprel) hydrochloride, although not consistent, is at times of value in increasing the ventricular rate.

Summary

The open-cardiotomy patient requires individualized attention. Our postoperative care is based upon three principles:

1. Establishment of a minimal metabolism to lessen cardiac work.
2. Establishment and maintenance of cardiovascular stability.
3. Establishment and maintenance of optimal respiratory function.

The postoperative complications are many; the most significant ones are: (a) a febrile course resembling a postmitral commissurotomy syndrome, (b) acute or subacute bacterial endocarditis, and (c) cardiac failure.

References

1. Effler, D. B.; Groves, L. K.; Sones, F. M., Jr., and Kolff, W. J.: Elective cardiac arrest in open-heart surgery; report of three cases. Cleveland Clin. Quart. **23**: 105-114, April 1956.
2. Kolff, W. J.; Effler, D. B.; Groves, L. K., and Moraca, P. P.: Elective cardiac arrest with potassium citrate during open-heart operations; report of thirty-seven cases. J.A.M.A. **164**: 1653-1660, Aug. 10, 1957.
3. Kolff, W. J.; Effler, D. B.; Groves, L. K.; Peereboom, G., and Moraca, P. P.: Disposable membrane oxygenator (heart-lung machine) and its use in experimental surgery. Cleveland Clin. Quart. **23**: 69-97, April 1956.
4. Effler, D. B.: Chylothorax; a conservative method of management. Cleveland Clin. Quart. **19**: 6-11, Jan. 1952.

INTERNAL FIXATIVE DEVICE FOR ANTERIOR FUSION OF LUMBAR SPINE

Preliminary Experimental Report

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SINCE Hibbs first proposed spinal fusion in 1911, the problems inherent in the operation have heretofore remained essentially unsolved. With the posterior approach, interlaminar or interspinous fusions with or without joint-facet fixation generally require a prolonged period of postoperative immobilization and an even longer period of convalescence. All of the various technics of fusion occasionally or frequently cause pseudarthrosis. Posterior fusion has an inherent mechanical disadvantage in that the support to the involved vertebrae is developed posterior to the axis of spinal flexion and extension; therefore, the everyday motion of flexion of the lumbosacral spine may cause distraction at the site of fusion. Since distraction predisposes to slow union or nonunion of bone, flexion of the spine following posterior spinal fusion must be prevented until the healing is complete.

To circumvent these problems and to permit early postoperative mobilization, anterior fusion of the spine, using a transperitoneal approach, has been proposed.[1] This procedure frequently has failed, presumably because motion has occurred at the site of intended fusion. There are conceptual advantages to the interbody site for spinal fusion. It offers a large surface area for fusion, and a sufficient amount of bone to permit intervertebral metallic fixation if this seems desirable. In patients of all ages, the blood supply in the cancellous bone of the vertebral bodies is excellent. Since the vertebral bodies are anterior to the axis of spinal flexion and extension, the normal motion of vertebral flexion is not only permissible in the early postoperative period but even desirable: this motion causes compression at the fusion site and enhances the union of the one vertebral body to the other.

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It is the purpose of this paper to record a new technic for anterior transperitoneal fusion of vertebral bodies, which utilizes an intervertebral clamp and a bone graft, and to report our preliminary experimental results with that technic.

Indications for Fusion

Many anatomic structures have been implicated in the etiology of low-back pain. Bone, cartilage, joint capsule, muscle, and ligament each has had its proponents. During the last 15 years, posterior displacement of an intervertebral disc in the low-lumbar area often has been a popular cause of low-back pain. In some patients having recurrent attacks of pain in the low back with irritation of the nerve root in one or both legs, roentgenograms show a narrowed intervertebral space. These degenerated intervertebral discs occur frequently in persons 40 years or more of age. When degenerated discs occur in persons younger than 40, they usually are the result of acute severe trauma or the late result of a laminectomy for removal of a disc.

Although narrowed intervertebral spaces frequently are observed in patients who are asymptomatic, they characteristically occur in those who have lumbosacral back pain, the severity of which is directly related to the amount of stress placed upon their backs. To avoid back pain, such a patient must restrict his activities. The pain generally will be relieved when the patient lies down or when his back is protected with a brace or corset. A patient having a degenerated intervertebral disc primarily has low-back pain and occasionally leg pain in the sciatic distribution. Contrariwise, a patient having a ruptured intervertebral disc primarily has leg pain in the sciatic distribution and occasionally back pain.

The candidate for spinal fusion is the patient with a degenerated lumbar disc who has frequent disabling low-back pain. This pain may be associated with some small amount of irritation of nerve root in the buttock and upper thigh, and tends to be precipitated by movements of the back and relieved by supporting the back or by lying down.

Technic of Fusion

There are four factors essential to the rapid union of bone regardless of location: (1) adequate blood supply, (2) adequate bone contact, (3) absolute immobilization until the bone is healed, and (4) absence of distraction even to the point of providing compression. A technic of arthrodesis of the intervertebral body has been developed to fulfill these requirements.

In brief, this technic consists of an anterior transperitoneal approach to the appropriate intervertebral disc space. The anterior common ligament is dissected away for visualization of the area, and the entire intervertebral disc and its remnants are excised. The opposing cortical plates of the adjacent vertebral bodies are removed, and the cancellous bone of the vertebral bodies is entered

to provide adequate blood supply. Bone contact is afforded by packing the created space with fragmented homogenous cancellous bone. Immobilization and compression are both attained through the use of the intervertebral clamp illustrated in Figure 1.

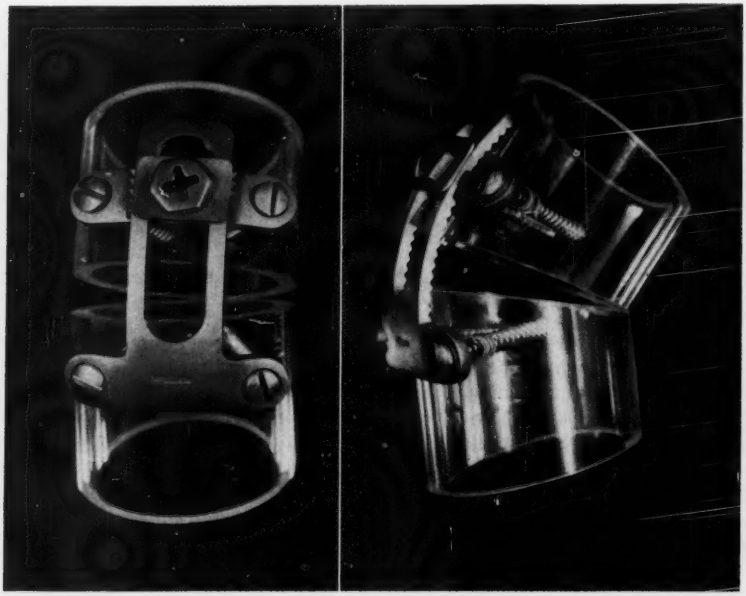

Fig. 1. Two views of the intervertebral clamp mounted on plastic tubing.

Experimental Data

Thirteen dogs, unselected adult mongrels of both sexes, were utilized in this study. Ten of the 13 dogs were operated upon according to the above-described technic utilizing an intervertebral clamp for immobilization, and the remaining 3 dogs underwent identical procedures with the exception that the internal fixative device was not employed. Immediately after fusion of two lumbar vertebrae, all 13 dogs were permitted volitional activity. All animals were sacrificed from 1 to 24 weeks after operation.

Each of the 10 dogs with internal metallic fixation had an uneventful course after surgery, and apparently moved about in a normal canine fashion. The postoperative course in each of the three control dogs was one of decreased and restricted motion with an apparent lack of desire to move and with some evidence of pain during the first few postoperative weeks.

In each dog at necropsy, the fused segment of spine including two vertebrae above and at least one below the arthrodesed joint was removed in toto and cleaned of surrounding soft tissue. Roentgenograms in both the anteroposterior and lateral projections were made, and the specimens were then fixed in Zenker's solution. The intervertebral clamps were removed from the fused segments, and these segments, together with those from the control animals, were bisected in the sagittal plane. In each of the 13 dogs, one of the halves thus obtained was kept as a gross specimen and the other was utilized for microscopic slides. Since all animals were sacrificed at relatively early stages of healing, stress studies were not performed.

The microscopic sections of the specimens from the 10 dogs in which internal fixation had been employed showed the typical progression through the various stages of endochondral bone formation. The sections of the specimens from the control dogs showed the typical progressive stages of the development of a pseudarthrosis.

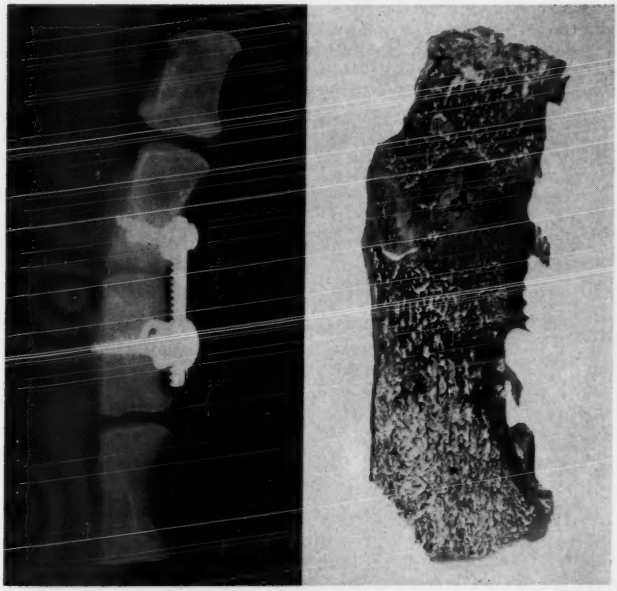

Fig. 2. (4-week specimen) *Roentgenogram:* Intervertebral space absent; vertebral cancellous plates absent. No evidence of osteogenesis. *Photomicrograph:* Defect between vertebral bodies bridged by granulation tissue containing cartilaginous islands (callus) and fragments of necrotic bone (bone-graft chips). Osteoblastic hyperplasia with early new-bone formation was present at margins of defect but is not visible in this photomicrograph. Hematoxylin-eosin—methylene blue; X 3½.

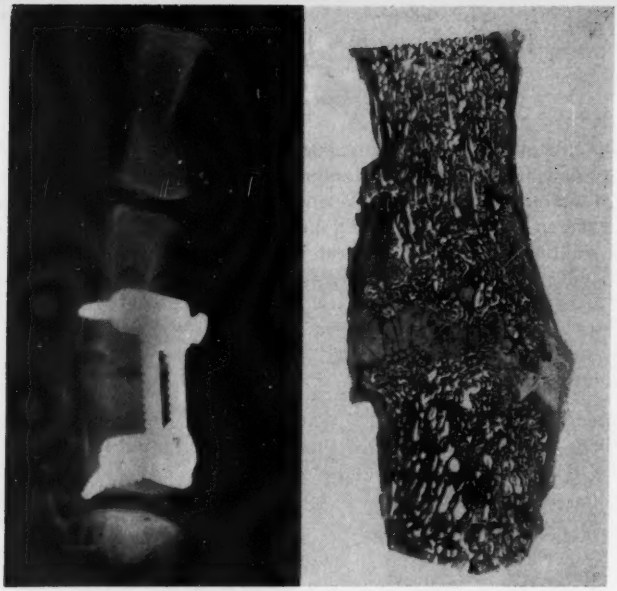

Fig. 3. (6-week specimen) *Roentgenogram:* Joint space obliterated; vertebral cancellous plates absent; no evidence of osteogenesis. There was no motion with clamp in place; free movement when it was removed. *Photomicrograph:* Vertebral bodies united by dense callus; in vicinity of defect the bone trabeculae are thickened and adjacent osteoid bars indistinct. Bone-graft chips are not evident. Hematoxylin-eosin—methylene blue; X 3½.

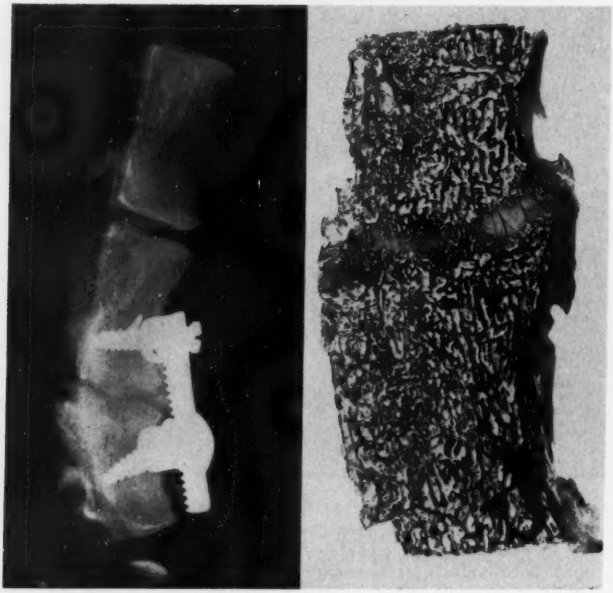

Fig. 4. (15-week specimen) *Roentgenogram:* Joint space obliterated; intervertebral cancellous bone plates absent; early bone formation seen in lateral view. An anteroposterior projection of the specimen showed lateral proliferation of bone at the site of fusion. Vertebral bodies were not movable one upon the other with or without fixative device. *Photomicrograph:* New bone trabeculae patchily unite the vertebral bodies; intervening cartilaginous islands present with foci of normal endochondral bone formation. Hematoxylin-eosin—methylene blue; X 3½.

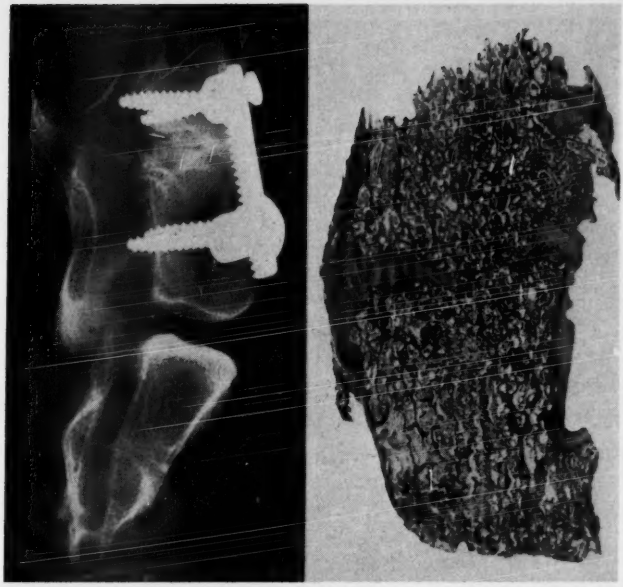

Fig. 5. (24-week specimen) *Roentgenogram:* On lateral projection there is completely normal bony architecture in the anterior one third of the fusion site; the posterior two thirds still shows lack of complete bony union, although some trabeculae appear to bridge the space. *Photomicrograph:* Further advancement of bony union, but still incomplete. Fibrocartilaginous islands present in posterior two thirds. After removal of clamp, union was solid. Hematoxylin-eosin—methylene blue; X 3½.

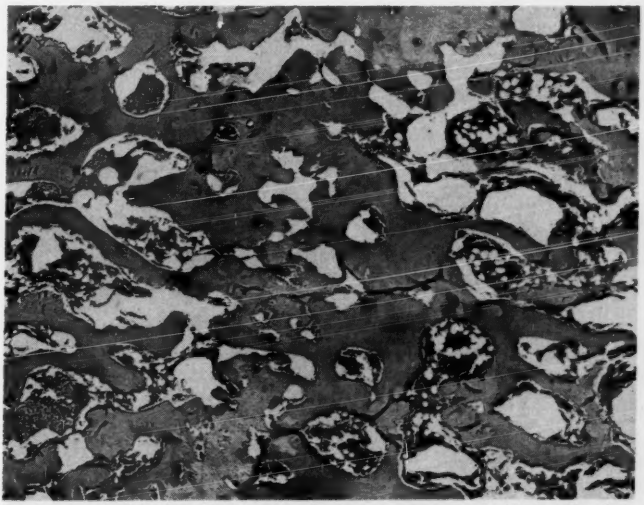

Fig. 6. Photomicrograph of a section taken from the anterior one third of the fusion site of the 24-week specimen showing the character of the bony union of the vertebral bodies. Small islands of fibrocartilage still are present superiorly and inferiorly in the photomicrograph. Hematoxylin-eosin—methylene blue; X 35.

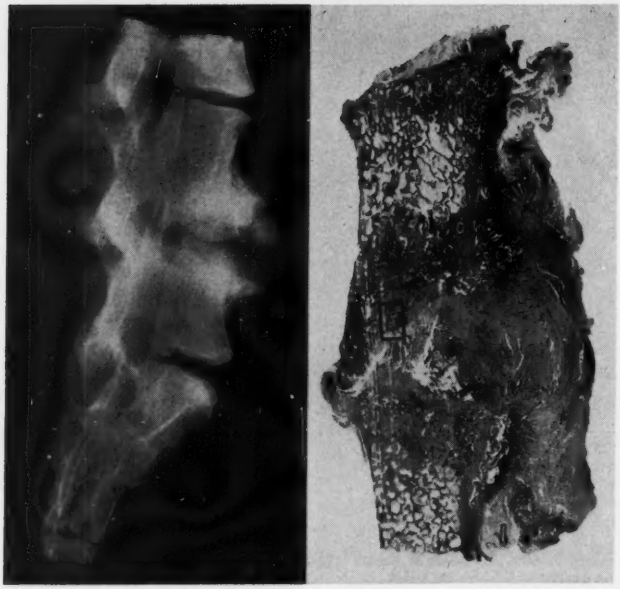

Fig. 7. (24-week control) *Roentgenogram:* Intervertebral space diminished; marked irregularity of joint space with scattered proliferation of new bone in general area in both anteroposterior and lateral projections. Obvious pseudarthrosis with some posterior luxation of the proximal vertebra on the distal. *Photomicrograph:* Peripherally, vertebral bodies joined by dense fibrous tissue; centrally, an excavation between the vertebral bodies containing necrotic bone spicules and old granulation tissue. Marked thickening of the ends of the vertebral bodies (eburnation) in part covered by an irregular layer of cartilage. Grossly, there was no stable union, the parts being readily movable on each other. Hematoxylin-eosin—methylene blue; X 3½.

Fig. 8. A higher power view of the area marked by the rectangle in Figure 7. Dense fibrous tissue, fibrocartilage, and granulation tissue are the principal components. In the center of the field are a few isolated bone trabeculae, partially surrounding the islands of granulation tissue. Hematoxylin-eosin—methylene blue; X 35.

For the purposes of this brief report, findings in only selected dogs are presented, namely those dogs in which necropsy was performed 4, 6, 15, or 24 weeks after the procedure with internal fixation, and 24 weeks after the procedure without internal fixation. The roentgenogram of the pathologic specimen and the low-power photomicrograph of the histologic section for each of these five dogs are shown in Figures 2 through 8. All the remaining animals showed a degree of bone formation that was consistent with the length of time between operation and sacrifice of the animal. Figures 9 and 10 show in chronologic order the roentgenograms and photomicrographs of the specimens from each of the five selected animals.

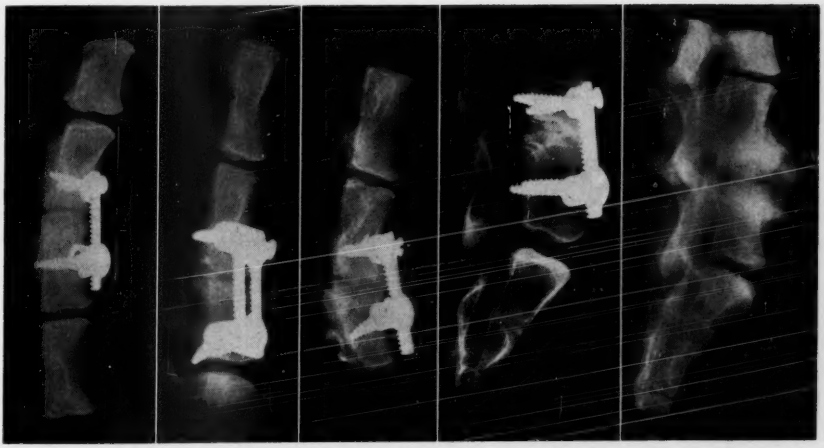

Fig. 9. A panorama of the lateral-view roentgenograms of the necropsy specimens arranged in chronologic order and showing the progression of bony union. From left to right, 4-week, 6-week, 15-week, and 24-week specimens, and 24-week control specimen.

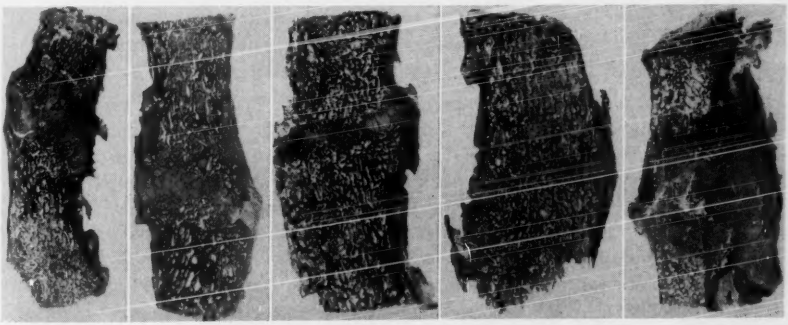

Fig. 10. A panorama of the photomicrographs of the necropsy specimens arranged in chronologic order. From left to right, 4-week, 6-week, 15-week, and 24-week specimens, and 24-week control specimen. Hematoxylin-eosin—methylene blue; X 3½.

Conclusions

A series of 10 dogs was operated upon utilizing a new technic of spinal arthrodesis based upon the concept that grafting of vertebral bodies combined with metallic fixation should provide a high incidence of successful fusion and a minimum of postoperative morbidity. Three additional dogs were operated upon in the same fashion but without the use of an internal fixative device. Each of the 10 dogs in which internal fixation was utilized showed the degree of healing that would be optimally expected for the duration of life permitted after operation. Each of the three control dogs developed or was developing pseudarthrosis, clearly indicating that adequate immobilization is essential for the consistent production of bone fusion between vertebral bodies. Further experimental fusions have been performed with the intent of studying results after one year.

Reference

1. Lane, J. D., Jr., and Moore, E. S., Jr.: Transperitoneal approach to intervertebral disc in lumbar area. Ann. Surg. **127**: 537-551, March 1948.

THE TREATMENT OF RHEUMATOID ARTHRITIS COMPLICATED BY CHRONIC HYPERCORTISONISM, AND THE THEORETICAL CAUSAL ROLE OF CERTAIN AMINE OXIDASES

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THE recognition by Hench, Kendall, Slocumb, and Polley[1] in 1948 of the desirable effects exerted by cortisone and corticotropin on inflammation and swelling in patients with rheumatoid arthritis and associated diseases is considered one of the great medical discoveries of our time. However, it has since become apparent that the effect of these hormonal agents is not specific, that the desirable effect is only temporary, and that acute or chronic hypercortisonism may ensue from overdosage. The undesirable effects that may occur have been described by Slocumb, Polley, Ward, and Hench,[2] and include alteration in electrolyte and water metabolism, decrease in carbohydrate tolerance, acneiform eruption, hirsutism, striae, deposition of fat, menstrual disorders, hyperacidity, delay in wound healing, and hypertension. Chronic overdosage is variously evidenced by emotional instability, increased fatigability and muscle aching, inability to concentrate, and depressed psychomotor activity. When these signs and symptoms are present, withdrawal of the corticosteroids may be extremely difficult, and must be accomplished slowly and gradually over a period of months; during this period, the patient must co-operate fully with the physician and must get 12 to 14 hours of sleep nightly together with extra periods of rest during the day.[2] Too rapid reduction in dosage may result in a flare-up of the rheumatoid arthritis, and in some patients, corticosteroid therapy may have to be continued indefinitely.[2]

Recently Scherbel, Schuchter, and Harrison[3] reported a method of administering a combination of chemotherapeutic agents to patients with progressive and persistently active rheumatoid arthritis. Despite decrease of corticosteroid dosage, these patients showed sustained improvement and few side effects. We have also used this method of therapy effectively in patients with rheumatoid arthritis in whom chronic hypercortisonism had resulted from long-term hormonal overdosage. In our opinion, these patients were not at all likely to develop spontaneous remissions during an abrupt reduction in dosage of corticosteroid. It, therefore, can be assumed that the drugs other than the corticosteroid altered the disease significantly.

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From our findings in patients having rheumatoid arthritis with or without hypercortisonism, we believe that the central nervous system manifestations of both conditions result from the same biochemical alterations but that these alterations are exaggerated in patients having rheumatoid arthritis with hypercortisonism. It is the purpose of this paper to report the results of treatment in 16 patients having rheumatoid arthritis with chronic hypercortisonism, and to suggest a theoretical explanation of some of the manifestations of rheumatoid arthritis.

Methods

Sixteen patients with active rheumatoid arthritis complicated by chronic hypercortisonism comprise the series. The group consists of 12 women—5 of whom were premenopausal and 7 of whom were postmenopausal—and 4 men. The ages of the women ranged from 33 to 66 years; those of the men from 47 to 62 years. The duration of rheumatoid arthritis ranged from 1 to 11 years. Twelve patients had stage 2 and four had stage 3 disease; 11 patients were classified as being functional class 3 and five as functional class 4, according to criteria of the American Rheumatism Association.[4] Each patient had characteristic features of chronic hypercortisonism, and all had been taking corticosteroids for periods ranging from six months to seven years, in amounts equivalent to or more than 20 mg. of prednisone per day. Table 1 summarizes the data on the 16 patients.

Clinical Features in Patients with Chronic Hypercortisonism

All these patients had been treated elsewhere with corticosteroids as the sole therapeutic agent and had developed resistance to the hormone. As response to the hormone diminished, 10 of the patients voluntarily increased steroidal dosage without medical advice or supervision. The most common complaints of all patients on admission here were severe weakness, fatigability, and generalized muscle aching. Round facies, supraclavicular and cervicodorsal fat pads, and weight gain were the most frequent physical findings. Fifteen patients had gained from 6 to 30 pounds in weight. Twelve patients had 2 to 4 plus dependent edema of the lower extremities. Joint swelling of varying degree and moderate-to-severe pain on motion were present in all patients and had become more severe as response to the corticosteroid had diminished. Nine were emotionally unstable and had cyclic swings in mood. Seven complained of increased nervous tensions and persistent insomnia. Five noted difficulty in concentration and five were in states of moderately severe depression at the time of initial examination. Four appeared to have greatly increased pain sensitivity that limited their activity. Six had epigastric distress manifested by nausea, burning, and low-abdominal pain. Four of these six had peptic ulcers; three were duodenal ulcers and one was an antral ulcer. All ulcers healed on medical management while

Table 1.—*Summary of data on 16 patients having rheumatoid arthritis and chronic hypercortisonism*

Case number	Sex; pre-menopausal or post-menopausal	Age, years	Duration of disease, years	Disease severity*		Duration of steroidal treatment	Initial response to steroids	Time before steroid "escape," months	Duration of hospitalization, days
				Stage	Functional class				
1	F; pre	38	1	3	3	7 mo.	Good	4	10
2	M	47	5	2	3	24 mo.	Poor	—	12
3	F; pre	33	2	2	3	7 mo.	Good	4	14
4	F; post	48	1	2	3	10 mo.	Good	3	12
5	M	54	6	2	3	10 mo.	Excellent	2	11
6	F; post	47	7	3	3	36 mo.	Good	12	14
7	F; pre	36	11	2	4	36 mo.	Good	8	14
8	M	51	4	2	3	12 mo.	Fair	2	14
9	F; post	49	1	2	3	9 mo.	Excellent	6	13
10	F; post	61	2	3	4	20 mo.	Good	11	29
11	F; post	66	4	2	3	48 mo.	Good	12	14
12	F; pre	43	6	2	4	6 mo.	Good	3	7
13	F; post	58	4	2	4	12 mo.	Poor	1-2	13
14	F; post	48	2½	3	3	20 mo.	Fair	2	12
15	F; pre	42	3	2	3	36 mo.	Good	9	15
16	M	62	10	2	4	7 yr.	Good	6	11

**Classification of American Rheumatism Association.*

Table 2.—*Symptoms and signs in 16 patients having rheumatoid arthritis with chronic hypercortisonism*

Case no.	Symptoms	Signs
1	Insomnia, irritability, increased nervous tension, fatigability, muscle aching, hyperalgesia, emotional instability	Weight gain, facial rounding, edema of lower extremities, multiple joint swellings, B.P. 140/85
2	Increased nervous tension, muscle aching, fatigability, insomnia, anorexia, hyperalgesia, irritability, emotional instability	Weight gain, facial rounding, edema of lower extremities, moderate plethora and osteoporosis, moderate multiple joint swellings, B.P. 100/68
3	Muscle aching, increased nervous tension, irritability, insomnia, depression, poor concentration, fatigability	Edema of lower extremities, facial rounding, weight gain, moderate osteoporosis, moderate swelling of joints of knees, ankles, wrists, B.P. 122/86
4	Insomnia, increased nervous tension, muscle aching, irritability, anorexia, increased pain sensitivity, fatigability, emotional instability	Facial rounding, plethora, edema of lower extremities, weight gain, moderate multiple joint swellings, B.P. 130/80
5	Muscle aching, increased pain sensitivity, activity restricted to chair, fatigability, emotional instability	Edema of lower extremities, facial rounding, supraclavicular and posterior cervical fat pads, weight gain, marked osteoporosis, duodenal ulcer, multiple joint swellings, B.P. 132/80
6	Insomnia, fatigability, muscle aching and weakness, depression and poor concentration, emotional instability	Facial rounding, supraclavicular and posterior cervical fat pads, edema of lower extremities, weight gain, marked osteoporosis, moderate swelling of joints of knees and ankles, B.P. 134/76
7	Insomnia, fatigability, muscle aching, hyperalgesia, nausea, vomiting, depression	Edema, facial rounding, plethora, weight gain, increased facial and body hair, marked multiple joint swellings, B.P. 112/76
8	Generalized muscle aching and soreness, weakness and fatigability, activity restricted to chair	Weight gain, facial rounding with plethora, supraclavicular fat pads, marked osteoporosis, duodenal ulcer, multiple joint swellings, B.P. 130/80

Table 2—continued

Case no.	Symptoms	Signs
9	Euphoria, increased nervous tension, muscle aching with hyperalgesia, poor concentration, fatigability, emotional instability	Facial rounding, plethora, edema of lower extremities, weight gain, multiple joint swellings, B.P. 140/60
10	Activity restricted to chair, fatigability, muscle aching, increased pain sensitivity, depression	Edema, facial rounding, plethora, weight gain, supraclavicular and posterior cervical fat pads, moderate multiple joint swellings, B.P. 110/70
11	Muscle aching with increased pain sensitivity, easy bruising, activity restricted to chair, increased fatigability	Weight gain, facial rounding, plethora, increased body and facial hair, edema of lower extremities, supraclavicular and posterior cervical fat pads, moderate osteoporosis, moderate multiple joint swellings, B.P. 160/80
12	Activity restricted to chair, hyperalgesia, increased fatigability, muscle aching, insomnia, nausea, emotional instability	Weight gain, facial rounding, supraclavicular fat pads, mild osteoporosis, mild multiple joint swellings, B.P. 120/70
13	Muscle aching in arms and legs, irritability, inability to concentrate, increased nervous tension, emotional instability, addiction to dihydromorphinone (Dilaudid) hydrochloride, fatigability	Weight gain, facial rounding, supraclavicular and posterior cervical fat pads, marked osteoporosis, moderate multiple joint swellings, gastric ulcer, B.P. 140/84
14	Generalized muscle aching, increased irritability and fatigability, increased nervous tension, poor concentration, insomnia, emotional instability	Facial rounding, weight gain, increased body and facial hair, edema of lower extremities, marked osteoporosis, duodenal ulcer, severe multiple joint swellings, B.P. 130/80
15	Generalized muscle aching, increased pain sensitivity, depression, increased fatigability, weakness, anorexia, easy bruising	Edema of lower extremities, weight gain, facial rounding, posterior cervical fat pads, plethora, severe multiple joint swellings, B.P. 116/74
16	Marked restriction of activity while taking steroid, muscle aching, increased fatigability, emotional instability, easy bruising	Weight gain, facial rounding, marked facial flushing, edema of lower extremities, supraclavicular fat pads, gynecomastia, marked osteoporosis with vertebral compression fractures, moderately severe multiple joint swellings, B.P. 126/78

administration of corticosteroids was maintained in a reduced dosage, never exceeding 7.5 mg. of prednisone daily. Table 2 summarizes the symptoms and signs in the 16 patients.

Blood pressures were not increased significantly; only one patient had a systolic pressure higher than 140 mm. Hg, and no patient had a diastolic pressure exceeding 90 mm. Hg. Four patients had fasting hyperglycemia, and in one of them control of the diabetes requires the use of insulin. Serum L.E. tests were performed in 14 of the 16 patients, while chronic hypercortisonism was present, and in all the tests were negative. In one patient the L.E. test became positive six weeks after combined treatment was started (at which time the patient showed excellent objective and subjective improvement). In the 16 patients the hemoglobin content of the blood ranged from 10 to 15 gm. per 100 ml., and the total leukocyte counts from 4,500 to 10,300 per cu. mm. Sedimentation rates were moderately to markedly elevated as determined by the Rourke-Ernstene method.[5] Serum polysaccharide concentrations[6] ranged from 176 to 268 mg. per 100 ml., with the ratio of polysaccharide to total protein[7] greater than 2.1 per cent in each instance.

Treatment

The patients in this study were hospitalized for periods averaging 13 days. In general, treatment varied only slightly among patients, and followed the pattern previously described.[3] Treatment was begun after laboratory studies were obtained; in all patients these included roentgenograms and determinations of peripheral blood counts, plasma protein and serum polysaccharide contents, erythrocyte sedimentation rates, and, in some patients, other special studies including peripheral blood L.E. and serum latex fixation tests.

Our concept of treatment has been described in earlier reports.[3, 8-11] Initially corticotropin and nitrogen mustard are administered to suppress rapidly the inflammation of rheumatoid arthritis. The antimalarial drugs and small doses of prednisone are given to maintain the disease suppression induced by intravenous corticotropin and nitrogen mustard. Iproniazid is administered to alleviate the central nervous system manifestations characteristic of rheumatoid arthritis and possibly to potentiate the effect of maintenance drugs.

Twenty-five milligrams of promazine hydrochloride* was injected intramuscularly and then aqueous corticotropin, 10 units in 500 ml. of 5 per cent dextrose in water, was intravenously administered. One-half hour later 2 mg. of nitrogen mustard** was injected into the intravenous tubing. Intravenous therapy was continued daily for five days, but on the second day the dose of nitrogen mustard was increased to 3 mg. and continued at this dose for the rest of the five-day period. On the initial day of intravenous therapy the oral dosage of corticosteroid was reduced immediately to 7.5 mg. of prednisone or its

Sparine hydrochloride, Wyeth Laboratories.

**Mustargen hydrochloride, Merck Sharp & Dohme, Division of Merck & Co., Inc.*

equivalent daily, and was further decreased as improvement became apparent. To maintain the suppression of the disease which resulted from the intravenous administration of ACTH and nitrogen mustard, one of the antimalarial agents, chloroquine phosphate** (250 mg. daily) in seven patients or hydroxychloroquine sulfate+ (200 mg. three times daily) in nine patients, was administered with the oral corticosteroid. The dosage of iproniazid++ initially was 50 mg. daily, which was gradually reduced as improvement in central nervous system manifestations occurred.

Intraarticular injections were given every other day to each patient with moderate-to-marked joint swelling. The wrists, knees, ankles, and occasionally the elbows and small joints of the fingers were injected from two to four times with combined nitrogen mustard—hydrocortisone tertiary-butylacetate ++ prepared as follows[8]: 0.5 mg. of nitrogen mustard diluted in 0.5 ml. saline solution was mixed with 1 ml. hydrocortisone acetate,† hydrocortisone tertiary-butylacetate, or prednisolone tertiary-butylacetate†† (25 mg. per milliliter).

After completion of five days of intravenous therapy the patients were observed for minor relapses while oral medication—prednisone, an antimalarial agent, and iproniazid—was continued. If muscle aching, weakness, or joint pain occurred within the first few days, corticotropin and nitrogen mustard were again administered intravenously, but the dose of nitrogen mustard was reduced to 1 mg. while the dose of corticotropin was maintained at 10 units added to 500 ml. of 5 per cent dextrose in water. The total dose of nitrogen mustard administered intravenously over a period of two weeks ranged from 14 to 17 mg. In patients with rheumatoid arthritis who had side effects from hormonal overdosage, the total white blood cell count was seldom altered by the dose of nitrogen mustard given. Lymphopenia appeared during the first few weeks of combined-drug therapy; we believe this condition primarily resulted from the action of nitrogen mustard although lymphocyte counts were somewhat low in 12 of the 16 patients before intravenous therapy was started.

Physical therapy was begun after the third day, when general strength had improved and muscle aching had diminished, and was continued throughout the period of hospitalization. During this time the patients also were given instructions for physical therapy to be carried out at home.

Orthopedic measures usually were carried out after the first week of therapy, when indicated, and shoes were fitted during the second week of therapy, after edema of the lower extremities had subsided.

Maintenance Therapy

Prior to discharge from the hospital the patients were instructed in the administration of depot corticotropin, which we believe is an important feature

**Aralen phosphate, Winthrop Laboratories.*
***Plaquenil sulfate, Winthrop Laboratories.*
+Marsilid phosphate, Hoffmann-La Roche, Inc.
++Hydrocortone-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.
†Hydrocortone acetate, Merck Sharp & Dohme, Division of Merck & Co., Inc.
††Hydeltra-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.

of the combined program of therapy.[3] During the two to four weeks after discharge from the hospital, 10 units was administered twice a week, after which 10 units was administered once a week; this dosage was maintained until the patient was asymptomatic. The dosage of prednisone was reduced from 7.5 mg. daily to 3 mg. daily after nine months of treatment in eight patients and after 13 months of treatment in three patients. Four patients have continued to receive 7.5 mg. daily and for one patient treatment was discontinued.

One of the antimalarial agents was administered with the corticosteroid to each of the patients, as previously described. Most of the patients have remained on maintenance therapy usually consisting of chloroquine phosphate, 250 mg. daily, or hydroxychloroquine sulfate, 600 mg. daily. The antimalarial agent was the last drug to be reduced in dosage and its administration was not stopped until after the patient had become asymptomatic and results of laboratory studies had been normal for three months.

The dosage of iproniazid was initially 50 mg. daily and after two to four weeks, depending upon improvement in central nervous system manifestations, it was reduced to 25 mg. daily. The dosage was decreased as elevation of mood became apparent; elevation in mood was directly associated with signs of recovery of autonomic balance and increased deep reflexes. The dosage usually was maintained for two to three months, after which time it was further reduced to and maintained at 10 mg. daily. Administration of iproniazid usually was stopped after the patient had recovered sufficiently to permit corticosteroid to be withdrawn.

Intraarticular injections were continued at monthly intervals until joint swelling subsided. Initially each of the 16 patients received intraarticular injections into one or more joints, and 15 of the 16 required at least one additional injection after discharge from the hospital. Usually intraarticular injections were not necessary after the second or third month of therapy.

Results

All patients improved significantly, both objectively and subjectively, while in the hospital for an average period of 13 days. Improvement manifested by decrease in muscle aching and stiffness and an increase in strength usually was observed after the first or second intravenous injection of corticotropin and nitrogen mustard. After three days, 12 patients had significant improvement in both subjective and objective manifestations characterized by less aching and stiffness, increased strength and appetite, less nervousness and insomnia, and elevation of mood without euphoria. Temperatures, if elevated before treatment, usually fell rapidly to normal within 24 hours after treatment had been begun and remained normal during the period of hospitalization. After five days of treatment, fatigability diminished almost completely in four patients and was apparent with moderate activity in four patients. The remaining eight patients responded less rapidly although improvement appeared in six patients after two weeks and in two patients after three weeks. Rounding of

the face, plethora, and fat pads in the supraclavicular and cervicodorsal regions began to diminish by the fifth day in most of the patients. After two weeks five patients lost the appearance characteristic of hormonal overdosage and in seven patients it was noticeably decreased. Only 3 of the 15 patients who continued therapy still had slight rounding of the face without plethora after two months of treatment. Each patient lost from 8 to 24 pounds in weight during the first month of treatment. Excess perspiration of the hands and feet was noted in nine patients and disappeared completely in four patients before they were discharged from the hospital; in the remaining five, it subsided within six weeks. Twelve of the 16 patients stated that they tolerated a cool environment better than they had previously. Serial intraarticular injections of hydrocortisone and nitrogen mustard and intravenous injections of corticotropin and nitrogen mustard were highly effective in rapidly reducing swelling and inflammation of the synovialis and adjacent connective tissue. Joint and tendon swelling with adjacent muscle spasm began to subside by the third day and in most instances was still apparent by the end of the first week of therapy. By the end of the second week most of the swelling had subsided in 13 of 16 patients and was reduced by more than half in three patients. After three weeks only 1 of the 16 patients had joint swelling that had not subsided satisfactorily.

Over-all improvement in most instances was characterized by an irregular and unpredictable course. Of the 15 patients in whom treatment was continued, two had a relapse two and three weeks, respectively, after leaving the hospital and both favorably responded quickly and without major incident to two intravenous injections of 10 units of aqueous corticotropin and 2 mg. of nitrogen mustard while administration of chloroquine phosphate, corticosteroid, and iproniazid was continued. In the remaining 13 patients, minor flares and relapses were frequent but never severe and appeared to be modified or incompletely suppressed. They became less severe and less frequent as each week passed. The one patient for whom treatment had to be discontinued, initially responded slowly but steadily and was apparently doing satisfactorily until six weeks after discharge from the hospital when she developed persistent nausea and anorexia from chloroquine phosphate. Her physician recently reported that she has not been able to continue taking either of the antimalarial agents.

Intraarticular injections were administered to nine patients for from two to three months at two to four week intervals because complete disappearance of joint swelling did not occur or swelling again appeared in one or more joints after activity had been increased. Joint swelling has subsided completely and has not returned in these nine patients.

Dosage of medication was reduced in six patients between the sixth and ninth months after treatment had begun; and in three of these patients the administration of corticosteroid was eventually stopped after one year and the patients have been satisfactorily maintained on an antimalarial agent for one year. Two years after the onset of combined treatment, the disease of four patients remains controlled with 7.5 mg. of prednisone daily in addition to an antimalarial agent and depot corticotropin 10 units weekly. Three patients have been receiving

treatment for nine months and in each the disease remains well controlled with only minor occasional muscle aching or stiffness and no recurrence of joint swelling. Two patients have been treated for less than six months and in each the disease remains satisfactorily controlled up to the present time. Twelve of the 15 patients show none of the clinical features characteristic of hormonal overdosage.

Toxicity reactions. Despite the use of multiple drugs, few toxicity reactions have occurred in our patients. We believe that the incidence of these reactions is low because the dose of each of the agents, with the exception of the antimalarial drugs, has been small.

The *antimalarial agents* caused a significant toxicity reaction in only one of our 16 patients. As noted above, that patient was unable to tolerate chloroquine phosphate or hydroxychloroquine sulfate because of persistent nausea and anorexia, and the combined therapy had to be terminated after six weeks. Two other patients had anorexia and mild nausea which subsided spontaneously after one month of treatment. In one patient receiving chloroquine phosphate a morbilliform dermatitis developed four weeks after therapy had been started; the dermatitis disappeared after administration of that drug was stopped but did not reappear during the subsequent administration of hydroxychloroquine sulfate. Hematologic abnormalities did not occur in any of these patients nor in any of the more than 650 other patients to whom we have given antimalarial agents.[8-11]

Iproniazid caused no toxicity reaction in any of the 16 patients. The drug was initially administered in small dosage. When increased neuromuscular tone (hyperactive deep tendon reflexes) was observed, the dosage was reduced. The dosage of iproniazid ranged from 50 mg. daily to 10 mg. every other day; once the maintenance dosage was established, it could be administered as long as necessary without causing toxicity reactions.

Transient nausea which was rarely associated with vomiting occurred in all patients after they had received *nitrogen mustard* intravenously, but this was easily controlled by the use of promazine hydrochloride.

Although occasional urticarial manifestations thought to be due to an allergic reaction to the intravenous use of *corticotropin* have been previously reported,[9] none of these 16 patients reacted in that manner. Administration of the *corticosteroids* caused no toxicity reactions in these patients.

Discussion:

Theoretical Role of Amine Oxidases

Patients having chronic progressive rheumatoid arthritis with chronic hypercortisonism constitute a therapeutic challenge. In most instances response to therapy heretofore has been disappointing and withdrawal symptoms have prevented rapid reduction in dosage of the corticosteroid. We believe that in

those patients cyclic swings in mood, emotional instability, and inability to concentrate are central nervous system manifestations characteristic of rheumatoid arthritis, appearing in an exaggerated state, and that the mesenchymal reaction is due to hormone "escape." The entire picture is further complicated by hypocorticalism resulting from the oral administration of cortisone or related hormones. Improvement in our patients was characterized by a decrease in both the mesenchymal reaction and the central nervous system manifestations.

Scherbel, Schuchter, and Harrison[3] have reported the effect of chemotherapeutic agents in patients having rheumatoid arthritis. Because of the characteristic response to these drugs, we postulate that certain biochemical alterations are present in rheumatoid arthritis with or without hypercortisonism.

The primary site of chemical or physicochemical action of adrenal steroids remains obscure although the crucial role of the hormones in the maintenance of homeostasis is well established. For the most part the actions of the cortical hormones have been described in terms of the response of other physiologic systems rather than in terms of primary mechanisms of action. It is generally agreed that patients with rheumatoid arthritis do not show quantitative or qualitative evidence of abnormalities of the adrenal steroids although it is possible that abnormalities are present in their intermediary metabolism. West[12] recently reported that in patients having rheumatoid arthritis there was no correlation between disease activity and the output of 24-hour urinary 17-hydroxycorticosteroids. He interpreted this finding to mean that the disease did not constitute a "stress" to the patient and questioned whether this in itself did not constitute a defect of the disease. He did not interpret this to mean that the corticosteroids played no part in the disease manifestations.

Iproniazid is one of the most consistently effective therapeutic agents that influences central nervous system manifestations characteristic of rheumatoid arthritis. Improvement is manifested by elevation in mood, generalized relaxation, disappearance of excessive sweating, and altered vasomotor reactivity. An increase in muscle tone and in muscle strength rapidly becomes apparent. However, constipation and decreased libido accompany the improvement. Because of the cumulative effect of iproniazid, deep tendon reflexes increase and muscle fasciculations appear after a few weeks to a few months of therapy. Swelling, redness, and tenderness, as well as aching and stiffness, of the joints do not subside rapidly; the gradual improvement in joint manifestations early in treatment usually can be related to increased rest and physical therapy. However, after from six to nine months of treatment, diminished disease activity usually is apparent. If toxicity reactions to overdosage of iproniazid occur—manifested by excitability, persistent clonus, and marked hyperactivity of deep reflexes—joint manifestations diminish, but again appear as toxicity subsides.

It has been shown by Zeller and Barsky[13] that iproniazid inhibits the activity of monoamine oxidase. The primary role of this copper-catalyzed enzyme is to inactivate amines, including serotonin, norepinephrine, and epinephrine. Recently, serotonin has been considered to enter into the functions of the autonomic and central nervous systems. Serotonin is believed to be necessary for normal mental processes, and interference with its action in the brain leads to

mental disorders and neurological dysfunction.[14] Brodie and Shore[15] have suggested that serotonin rather than acetylcholine may be the neurohormonal agent for the central parasympathetic system and that norepinephrine may be the chemical transmitter of the central sympathetic system.

If the concept proposed by Brodie and Shore is correct and if the effect of iproniazid which we have observed in patients with rheumatoid arthritis is confirmed, it is possible that the over-all effects in these patients are manifested by alterations in activity of amine oxidases or in metabolic alterations of one or more of the various amines inactivated by amine oxidases.

Although we believe that the biochemical alterations involved in rheumatoid arthritis are more complicated than described here, for the sake of simplicity we base our concept on the unproven view that a major biochemical defect in rheumatoid arthritis may involve amine oxidases or one or more of the various amines inactivated by the oxidases or both. The clinical features characterizing rheumatoid arthritis can be divided into two groups: those resulting from or resembling the effect of increased activity of amine oxidases within the central nervous system; and those resulting from or resembling the effect of decreased activity of amine oxidases within tissues outside the central nervous system, primarily mesenchyme. Increased oxidase activity within the central nervous system, by inactivating serotonin and other amines, could cause the many and varied central nervous system manifestations characteristic of rheumatoid arthritis. Diminished activity of serotonin would result in depressed psychomotor activity, emotional instability, and other mental aberrations characteristic of rheumatoid arthritis. A delay in transmission of nerve impulses would occur across synapses in the central sympathetic and parasympathetic autonomic nervous system, resulting in autonomic imbalance. Delayed transmission of impulses through cholinergic somatic nerves to muscle would account in part for muscle weakness or atrophy and diminished deep reflexes.

Michotte[16] has reported that the excretion of norepinephrine is decreased in patients with rheumatoid arthritis, resulting in an altered excretion ratio of norepinephrine to epinephrine. He also found that an infusion of 0.1 per cent procaine hydrochloride, a potent inhibitor of monoamine oxidase, caused an increase in the excretion of norepinephrine, resulting in a normal ratio of norepinephrine to epinephrine.

The second group of clinical features involve tissues outside the central nervous system, primarily mesenchyme. The reaction characterized by inflammation and proliferation of connective tissue can be explained theoretically by alterations in the oxidases and amines that are the reverse of those previously described within the central nervous system. In the peripheral tissues the amine oxidases would be decreased, causing increased activity of tissue serotonin. We feel that there is at least suggestive evidence that serotonin in the tissues can act as an irritant and produce an inflammatory action and may act as a stimulant of connective tissue and produce fibroblastic proliferation. The various mechanisms of action that have been considered will not be discussed here except to state that we have observed an acute synovial reaction following the local injection of minute amounts of serotonin. These will be reported in

detail elsewhere. Numerous descriptions of fibrotic right-sided valvular heart lesions and fibrous tissue masses surrounding pelvic organs and low-abdominal arteries have been reported in patients with metastatic carcinoid tumors, suggesting a correlation between serotonin and proliferation of fibrous tissue.

The high incidence of relapse in patients having rheumatoid arthritis treated with a corticosteroid, and the central nervous system manifestations following hormonal overdosage indicate that the hormones alone are not capable of adequately suppressing the disease activity. The activity of various neurohormonal agents appears to be progressively diminished during corticosteroid therapy, further indicating that the adrenocortical hormones do not prevent increased oxidase activity or diminished neurohormonal amine activity in the central nervous system.

Significant improvement appeared in our patients coincident with apparently increased neurohormonal activity which resulted from the administration of the amine-oxidase inhibitor iproniazid. This improvement allowed a reduction in the dosage of corticosteroid, further emphasizing the relationship between the adrenal corticosteroids and the neurohormonal agents.

The effect of the antimalarial agents (chloroquine phosphate and hydroxychloroquine sulfate) in patients with rheumatoid arthritis has not been established, but it is our opinion that their primary action is on tissues outside the central nervous system, and that these drugs should be used for long-term maintenance therapy. We have discussed the action of nitrogen mustard previously.[8,9] It is of primary importance in producing rapid suppression of joint inflammation after which time disease activity is more easily controlled.

In the past, numerous nonspecific therapeutic agents have been recommended for treatment of rheumatoid arthritis but none has been found completely satisfactory. It is possible that many of these agents temporarily influenced certain amines or amine oxidases resulting in transient suppression of disease activity. We believe that further work is necessary to clarify the role of the amine oxidases and the various amines in rheumatoid arthritis and many other diseases.

Summary

The findings and results of treatment in 16 patients having rheumatoid arthritis complicated by hypercortisonism indicate that therapeutic agents other than corticosteroids have a significant effect in such patients. Improvement in each of these patients began a few days after initiation of combined-drug therapy although the dosage of corticosteroid had been rapidly reduced.

We believe that the central nervous system manifestations in patients with rheumatoid arthritis are the result of certain biochemical alterations that are exaggerated in patients having rheumatoid arthritis with hypercortisonism.

We have divided the clinical features characterizing rheumatoid arthritis into two groups: those manifest in the central nervous system and those in tissues outside this system. It has been theorized that the central nervous system manifestations result from, or resemble the effect of, increased activity of amine

oxidases or decreased activity of the neurohormonal amines or a combination of these actions. Outside the central nervous system, manifestations appear primarily in the mesenchymal tissues, and result from, or resemble the effect of, decreased activity of amine oxidases or increased peripheral activity of certain amines or both.

References

1. Hench, P.S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions; study in clinical physiology. Arch. Int. Med. **85**: 545-666, April 1950.
2. Slocumb, C. H.; Polley, H. F.; Ward, L. E., and Hench, P. S.: Diagnosis, treatment and prevention of chronic hypercortisonism in patients with rheumatoid arthritis. Ann. Int. Med. **46**: 86-101, Jan. 1957.
3. Scherbel, A. L.; Schuchter, S. L., and Harrison, J. W.: V. Chemotherapy in rheumatoid arthritis: concept. Cleveland Clin. Quart. **24**: 105-115, April 1957.
4. Steinbrocker, O.; Traeger, C. H., and Batterman, R. C.: Therapeutic criteria in rheumatoid arthritis. J.A.M.A. **140**: 659-662, June 25, 1949.
5. Rourke, M. Dorothy, and Ernstene, A. C.: Method for correcting erythrocyte sedimentation rate for variations in cell volume percentage of blood. J. Clin. Invest. **8**: 545-559, June 1930.
6. Shetlar, M. R.; Foster, J. V., and Everett, M. R.: Determination of serum polysaccharides by tryptophane reaction. Proc. Soc. Exper. Biol. & Med. **67**: 125-130, Feb. 1948.
7. Payne, R. W.; Shetlar, M. R.; Bullock, J. A.; Patrick, D. R.; Hellbaum, A. A , and Ishmael, W. K.: Serum polysaccharide-protein ratio (PR) as measure of rheumatoid arthritis activity. Ann. Int. Med. **41**: 775-779, Oct. 1954.
8. Scherbel, A. L.; Schuchter, S. L., and Weyman, S. J.: II. Intraarticular administration of nitrogen mustard alone and combined with a corticosteroid for rheumatoid arthritis; experimental and clinical studies. Cleveland Clin. Quart. **24**: 78-89, April 1957.
9. Scherbel, A. L.: I. Intravenous administration of nitrogen mustard alone and with corticotropin for rheumatoid arthritis. Cleveland Clin. Quart. **24**: 71-77, April 1957.
10. Scherbel, A. L.: III. Effect of isoniazid and iproniazid in patients with rheumatoid arthritis. Cleveland Clin. Quart. **24**: 90-97, April 1957.
11. Scherbel, A. L.; Schuchter, S. L., and Harrison, J. W.: IV. Comparison of effects of two antimalarial agents, hydroxychloroquine sulfate and chloroquine phosphate, in patients with rheumatoid arthritis. Cleveland Clin. Quart. **24**: 98-104, April 1957.
12. West, H. F.: Corticosteroid metabolism and rheumatoid arthritis. Ann. Rheumat. Dis. **16**: 173-182, June 1957.
13. Zeller, E. A., and Barsky, J.: In vivo inhibition of liver and brain monoamine oxidase by 1-isonicotinyl-2-isopropyl hydrazine. Proc. Soc. Exper. Biol. & Med. **81**: 459-461, Nov. 1952.
14. Wooley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin. Brit. M. J. **2**: 122-125, July 17, 1954.
15. Brodie, B. B., and Shore, P. A.: On Role for Serotonin and Norepinephrine as Chemical Mediators in Central Autonomic Nervous System. *In*, Hormones, Brain Function, and Behavior, edited by Hudson Hoagland. New York: Academic Press, Inc., 1957, pp. 161-176.
16. Michotte, L. J.: Reversal of urinary excretion ratio noradrenaline/adrenaline in rheumatoid arthritis. Programme Volume II, Ninth International Congress on Rheumatic Diseases, June 23 to 28, 1957, p. 326.

MALUNITED FRACTURE OF THE DISTAL ENDS OF THE RADIUS AND THE ULNA CORRECTED BY OBLIQUE RESECTION OF THE DISTAL END OF THE ULNA

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A FRACTURE that involves the distal ends of the radius and the ulna is one of the most common fractures that the general practitioner, the general surgeon, or the orthopedist is called upon to treat. If good function of the wrist joint is to be obtained, satisfactory reduction of the fracture must be accomplished. Good function of the traumatized wrist joint depends on four conditions: (1) restoration of normal length to the shortened radius, (2) correction of the dorsal angulation of the distal radial fragment, (3) relocation of the deviated distal radial or ulnar fragment, and (4) restoration of a normal, anatomic relationship between the radial-ulnar articulation. Failure to accomplish this last condition alone will cause progressive, traumatic changes that lead to loss of function of the wrist joint; and motion, particularly pronation and supination, may be severely limited.

The purpose of this paper is to: (1) illustrate, through a case presentation, the functional disability that may result at the wrist from a malunited fracture of the distal end of the ulna; (2) emphasize the value of distal ulnar resection to restore adequate function of the wrist joint, particularly pronation and supination; and (3) point out the value of making an oblique osteotomy resection of the distal end of the ulna in order to preserve the ulnar collateral ligament and thereby prevent instability of the wrist joint.

Report of a Case

A 39-year-old missionary nurse sustained a fracture of the distal end of the left radius and ulna in an automobile accident in June 1956. On the day of injury, a closed reduction was performed under general anesthesia and the fracture was immobilized for six weeks in a circular forearm cast that extended from the midpalmar crease to below the elbow. Ten months after reduction, all motions of the left wrist were normal except pronation, which was 60 degrees, and supination which was from 10 to 15 degrees. Roentgenograms of the left wrist revealed an apparently malunited fracture of the distal ulna and a healed fracture of the distal radius (Fig. 1). On May 9, 1957, resection of the distal end of the ulna was performed (Fig. 2). One month following surgery, the patient had full pronation of the left wrist, having gained 30 degrees of pronation

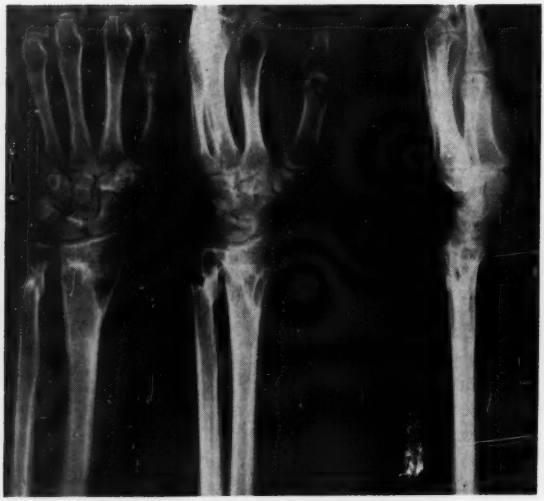

Fig. 1. Roentgenogram showing malunited fracture of the distal end of the left ulna and a healed fracture of the distal end of the radius. The length of the radius has been preserved.

Fig. 2. Roentgenogram after an oblique osteotomy resection of the distal end of the left ulna. This operation preserves the ulnar collateral ligament, and thereby prevents instability at the wrist joint.

(Fig. 3). She had 60 degrees of supination, an increase of 45 degrees of motion (Fig. 4). All other wrist motions still were normal.

Fig. 3. Photograph showing full pronation four weeks after oblique resection of the distal end of the left ulna.

Fig. 4. Photograph showing 60 degrees of supination four weeks after distal ulnar resection.

Discussion

When a fracture of the distal end of the radius or of the distal end of the radius and the ulna malunites, traumatic changes frequently occur at the radial-ulnar articulation. The sequelae are pain and limited motion of the wrist joint. Loss of optimal pronation or supination is a severe functional disability that to a great extent can be corrected by resection of the distal end of the ulna.

Boyd and Stone[1] in 1944 reported the results of resection of the distal end of the ulna as performed by various members of the Campbell Clinic. Of the 22 resections performed, in no case was motion of the wrist joint worsened. In fact, motion of the wrist, particularly pronation and supination, was improved in all.

Where there is shortening of the radius with a prominent ulnar styloid process, resection of the distal end of the ulna greatly improves the cosmetic appearance of the wrist. Resection of the ulnar styloid process in the absence of radial shortening alters the appearance of the wrist, but this is of little cosmetic importance. The muscle power in the hand and wrist may be only slightly decreased, following resection of the distal end of the ulna.

The success of distal ulnar resection in restoring function to the wrist joint, in large measure depends on how long the malunion has existed. Resection of the distal end of the ulna which is performed within 12 months of malunion, produces better functional results than does resection performed a year or more after the initial injury.

Summary

Malunited fractures of the distal end of the radius and the ulna commonly cause functional disability of the wrist joint.

Resection of the distal end of the ulna is a relatively simple surgical procedure. It will increase motion of the wrist joint, particularly pronation and supination, if it is performed soon after malunion of the distal ends of the radius or the ulna.

Reference

1. Boyd, H. B., and Stone, M. M.: Resection of distal end of ulna. J. Bone & Joint Surg. **26**: 313-321, April 1944.

THE ZINC SULFATE TURBIDITY TEST AND LIVER DISEASE

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THE zinc sulfate turbidity test has become a useful test in the diagnosis of liver disease because of its simplicity and reliability in detecting increased gamma-globulin levels. The zinc sulfate turbidity test was introduced in 1947 by Kunkel[1] as a simple means of determining the serum gamma-globulin level. However, the zinc sulfate turbidity test has not been used so extensively as the other turbidity and flocculation tests (cephalin and thymol) for liver function. This paper proposes to show the value and usefulness of the zinc sulfate turbidity by reviewing results of tests performed on patients at the Cleveland Clinic.

The results of zinc sulfate turbidity tests were compared with the clinical diagnoses in over 1,200 patients.[2] The diagnoses of these patients were divided into seven categories as follows: (1) normal or no evidence of organic disease; (2) noninfectious, nonhepatic diseases; (3) cirrhosis; (4) hepatitis; (5) obstructive jaundice; (6) infectious diseases; and (7) metastatic hepatic disease. The method of performing the zinc sulfate turbidity tests was the same as that originally described by Kunkel.[1]

Figure 1 represents the results of tests on 391 patients considered normal or having functional complaints with no evidence of organic disease. The mean zinc sulfate turbidity value was 6.42 $\pm$ 2.54 units. This study did not differentiate test results with regard to race, however, only a few patients were Negroes.[3] Only eight patients had turbidity values higher than 12 units. Studies on more than 200 apparently healthy blood bank donors ranged from 2 to 12 units with one exception. This donor had a value of 16 and later was found to have an ovarian cyst. Two months after the cyst was removed the zinc sulfate turbidity value was normal.

The results of tests on 510 patients with noninfectious, nonhepatic organic disease are also summarized in Figure 1. The mean was 7.78 $\pm$ 7.28 units. Tests done on 57 patients (11.2 per cent) gave values greater than 12 units. Four patients with multiple myeloma had the highest values (80, 73, 72, and 64 units). These four patients had very high gamma-globulin fractions in addition to greatly elevated serum globulin levels. In 12 other patients with values of 19 units or higher, there were 4 cases of ulcerative colitis, 3 cases of rheumatoid arthritis, and a case each of hemolytic anemia, myelofibrosis, lymphoblastoma,

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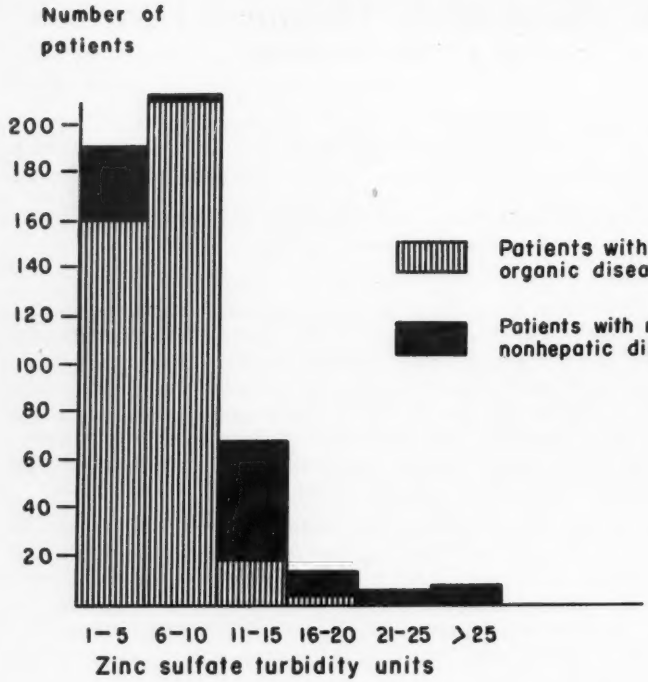

Fig. 1

essential hypertension, and nephritis. All of these conditions can be associated with an elevated level of gamma-globulin.

The results of tests done on 186 patients with hepatic cirrhosis are summarized in Figure 2. Values are included from all stages of both Laennec's and postnecrotic cirrhosis. Of the 186 tests, 122 (65.6 per cent) were higher than 12 units, and 57 (30.6 per cent) of the 122 were higher than 20 units. The mean was 17.10 $\pm$ 8.80 units. In our laboratory the zinc sulfate turbidity value is elevated more often in chronic hepatic disease than are the results of other turbidity or flocculation tests. The zinc sulfate turbidity test has its greatest usefulness in the diagnosis of cirrhosis, and usually the more chronic the disease the higher the value.

Figure 2 also summarizes zinc sulfate turbidity tests in 54 patients having infectious hepatitis. Of the 54, 20 (37 per cent) were found to have elevated zinc sulfate turbidity values. The highest values were seen in chronic or recurrent hepatitis, which suggests that each recurrence or exacerbation of the disease results in an increased antibody titer.

Zinc sulfate turbidity values were usually not elevated in patients having obstructive jaundice. Only 4 (9.5 per cent) of 42 patients in this group had

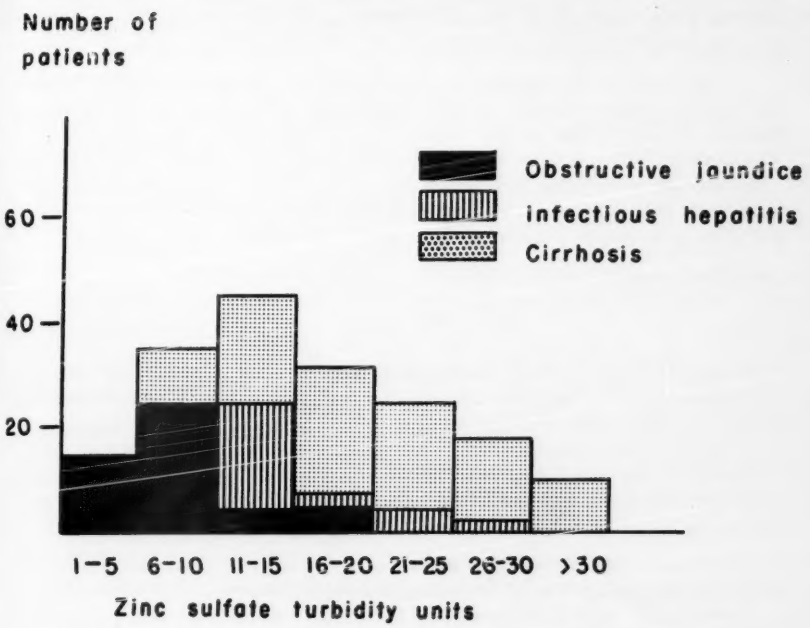

Fig. 2

values higher than 12. Of these four, one patient with a zinc sulfate turbidity of 18 units had a carcinoma of the ampulla of Vater with hepatic failure which probably accounts for the elevated results. In this group were included four patients having chlorpromazine jaundice; all four showed normal zinc sulfate turbidity values. The zinc sulfate turbidity is most significant when it is normal in the presence of long-standing jaundice in indicating an obstruction of the bile duct rather than a hepatocellular cause of the jaundice.[4] The values in obstructive jaundice, however, are no lower than normal. Like the other liver function tests, the zinc sulfate turbidity test does not differentiate extrahepatic from chlorpromazine jaundice.[5]

Zinc sulfate turbidity values were elevated in 4 of 12 patients with infectious disease and in 2 of 14 with hepatic metastasis. These elevated results probably reflect the gamma-globulin values associated with high rate of antibody formation.

Of the 1,200 patients whose results were reviewed, 13 had zinc sulfate turbidity values of 1 unit or lower. Of these 13 patients, 9 had advanced renal disease, 1 had idiopathic acquired hemolytic anemia, 2 had metastatic cancer, and 1 had chlorpromazine jaundice and arteriosclerotic heart disease with congestive failure. Electrophoretic studies showed in 80 per cent of these

patients a low total protein and a low gamma-globulin. Hayles[6] has reported low zinc sulfate turbidity values in patients with agammaglobulinemia.

Comparison of 174 zinc sulfate turbidity tests with electrophoretic studies gave a correlation coefficient of 0.59 between zinc sulfate turbidity and gamma-globulin. This is similar to the coefficient of 0.67 found by De la Huerga and his associates.[7] A somewhat better correlation, 0.63, was found when albumin —gamma-globulin ratios were compared with results of the zinc sulfate turbidity test. No significant correlation could be shown between albumin, alpha-globulin, or beta-globulin and the zinc sulfate turbidity.[2]

Discussion

The zinc sulfate turbidity is elevated in any disease in which the gamma-globulin is elevated. As liver disease becomes more chronic, gamma-globulin levels rise with resulting abnormal zinc sulfate turbidity. The zinc sulfate turbidity is higher in cirrhosis which follows infectious hepatitis than in nutritional or alcoholic cirrhosis.[8] The zinc sulfate turbidity test may not reflect small variations in gamma-globulin but can be depended upon to detect gross elevations.

The zinc sulfate turbidity is within normal limits in obstructive jaundice. When the zinc sulfate turbidity remains normal in the presence of jaundice there is a strong indication for surgery. On the other hand, an elevated zinc sulfate turbidity with jaundice may indicate a hepatocellular jaundice and warrants watchful medical management rather than surgery.

The zinc sulfate turbidity test may be of value in the diagnosis of low gamma-globulin levels. Although no patient with agammaglobulinemia was studied here, the zinc sulfate turbidity should be helpful in its detection.

Summary

Over 1,200 clinical diagnoses and zinc sulfate turbidity tests were compared to evaluate the zinc sulfate turbidity as an aid in the diagnosis of hepatocellular disease. The zinc sulfate turbidity test is valuable in the diagnosis of chronic liver disease, particularly cirrhosis. It is of value in the follow-up of hepatitis, becoming elevated if the disease becomes chronic. The zinc sulfate turbidity test is especially valuable in the differential diagnosis of long-standing jaundice —when within normal limits it indicates biliary obstruction and when elevated it may indicate hepatocellular disease.

The zinc sulfate turbidity correlates well with gamma-globulin as determined by electrophoretic protein studies. It can be used as a semiquantitative approximation of the gamma-globulin where electrophoretic protein studies are not available.

References

1. Kunkel, H. G.: Estimation of alterations of serum gamma globulin by turbidimetric technique. Proc. Soc. Exper. Biol. & Med. **66**: 217-224, Oct. 1947.
2. Wilson, T. E.; Brown, C. H., and Hainline, A., Jr.: Zinc sulfate turbidity test. Gastroenterology **32**: 483-493, March 1957.
3. Long, W. H.; Nassif, R.; Yonan, V., and Reinhold, J. G.: Further studies of racial differences in serum gamma globulin concentrations. Clinical Chemistry **2**: 238-239, Aug. 1956.
4. Popper, H.; de la Huerga, J.; Steigmann, F., and Slodki, M.: Turbidimetric gamma globulin determinations in hepatobiliary diseases. J. Lab. & Clin. Med. **35**: 391-402, March 1950.
5. Van Ommen, R. A., and Brown, C. H.: Obstructive-type jaundice due to chlorpromazine (Thorazine); report of three cases. J. A. M. A. **157**: 321-325, Jan 22, 1955.
6. Hayles, A. B.: Agammaglobulinemia. M. Clin. North America **40**:1203-1208, July 1956.
7. de la Huerga, J.; Popper, H.; Franklin, M., and Routh, J. I.: Comparison of results of gamma globulin and zinc sulfate turbidity tests with electrophoretic determination of gamma globulins. J. Lab. & Clin. Med. **35**: 466-474, March 1950.
8. Kunkel, H. G.; Ahrens, E. H., Jr., and Eisenmenger, W. J.: Application of turbidimetric methods for estimation of gamma globulin and total lipid to study of patients with liver disease. Gastroenterology **11**: 499-507, Oct. 1948.

THE CALCIFIED PINEAL BODY AND CARCINOMA

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THE pineal body or epiphysis is one of the controversial body structures as regards function. However, recent investigation supported by morphologic evidence suggests that the pineal body serves as an endocrine gland,[1] and that it may have an antigonadotropic activity.[2] Because anatomic and physiologic changes have been noted in the endocrine glands of patients with certain carcinomas, it was thought worthwhile to study the pineal body in a series of patients having carcinoma. Since there are no known means of determining or measuring the function of the pineal body, the investigation was limited to roentgen study of pineal calcification. It is the purpose of this paper to record the roentgen findings of pineal calcification in a selected series of patients having carcinoma and those in a control group of patients not having malignant neoplasm.

Material and Method

Selection of patients. All patients having metastatic carcinoma of the brain or skull and all patients having primary carcinoma of the breast, or of the head and neck, who were examined at the Cleveland Clinic between October 30, 1945, and October 27, 1954, were selected for the initial survey. In a review of the charts of 1,172 patients, 164 were found which listed available skull roentgenograms. These 164 patients comprised the *malignant group* for this study. The sites of their primary carcinomas were as follows: breast, 73 patients; lung, 34; prostate, 12; mouth, nose, and throat, 12; lower gastrointestinal tract, 6; upper gastrointestinal tract, 3; pancreas and bile ducts, 3; kidney, 3; uterus and cervix, 3; thyroid, 1; trachea, 1; primary unknown, 13.

None of the patients in the malignant group was less than 30 years of age. Consequently, the 110 patients not having malignant disease who were selected

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as the *control group* for this study were 30 or more years of age and had roentgenography of the skull during the month of January 1953.

Evaluation of roentgen findings. On roentgenograms, pineal calcification usually is seen in the midline above and slightly posterior to the petrous portion of the temporal bone, either as a small single opacity, or as an ovoid cluster, 0.5 to 1.0 cm. in diameter, composed of small calcified areas.[3] In the present study, calcification that was not present in the midline of this region was considered to be outside of the pineal body. To assure consistent, objective evaluation, all roentgenograms for the survey were interpreted by one radiologist (T.F.M.), who was uninformed as to the previous diagnoses.

Results

For purposes of comparison, the charts of both groups of patients were separated into subgroups on the bases of age and sex of the patient (Table 1).

Malignant group. Pineal calcification was present in 108 (65.9 per cent) of the 164 patients, occurring in 48 (66.7 per cent) of the 72 men, and in 60 (65.2 per cent) of the 92 women (Table 1).

Control group. Pineal calcification was present in 64 (58.2 per cent) of the 110 patients, occurring in 40 (69.0 per cent) of the 58 men, and in 24 (46.2 per cent) of the 52 women (Table 1).

Evaluation of Results

The determinable factors that could have influenced pineal calcification in these patients were: sex, age, history of pregnancy, presence of carcinoma.

Sex. In the control group, the incidence of pineal calcification in men (69.0 per cent) was significantly greater than that in women (46.2 per cent). The difference is significant at the 5 per cent level of confidence.[4]

Age. The mean age of the women with carcinoma was 51.9 years, and the mean age of the women without cancer was 48.3 years. There was, however, a greater difference between the mean ages of the two groups of men; the mean age of the men in the malignant group was 63.6 years and that of those in the control group was 45.0 years.

History of pregnancy. The incidence of pineal calcification has been reported to be higher in women who have been pregnant,[5] but pregnancy as a factor did not appear to influence the over-all incidence of pineal calcification in the women of this series. In the control group of 52 women, marital histories were available in 48, 39 of whom had been pregnant. Pineal calcification was present in 18 of the 39 women who had been pregnant, and in 4 of the 9 who never had been pregnant. Similarly, in the malignant group, of the 84 women with available marital histories, 64 had been pregnant and pineal calcification was present in 41 (64.1 per cent) of them; and of the 20 women who never had

Table 1.—*Age and sex distribution and incidence of pineal calcification in malignant group of 164 patients and in control group of 110 patients*

Age range, years	Malignant group, no. of patients						Control group, no. of patients					
	Sex		Pineal calcif.		No pineal calcif.		Sex		Pineal calcif.		No pineal calcif.	
	M.	F.	Men	Women	Men	Women	M.	F.	Men	Women	Men	Women
30-39	0	11	0	8	0	3	21	19	14	7	7	12
40-49	15	27	8	16	7	11	11	13	9	8	2	5
50-59	27	32	18	22	9	10	14	15	9	7	5	8
60-69	24	19	18	11	6	8	9	4	6	2	3	2
70-79	6	3	4	3	2	0	3	1	2	0	1	1
Total	72	92	48	60	24	32	58	52	40	24	18	28
Total	**164**		**108(65.9%)**		**56(34.1%)**		**110**		**64(58.2%)**		**46(41.8%)**	

been pregnant, pineal calcification was present in 13 (65 per cent). The incidence (75 and 76 per cent) of pregnancy in both groups also is similar.

Presence of carcinoma. The incidence of pineal calcification in the 72 men in the malignant group (66.7 per cent) approximates that in the 58 men in the control group (69.0 per cent). However, 60 (65.2 per cent) of the 92 women in the malignant group had calcified pineal bodies as compared with 24 (46.2 per cent) of the 52 women in the control group. This difference is significant at the 5 per cent level of confidence.* This unexpected finding prompted further study of the records of the women with carcinoma.

Seventy-one (77.2 per cent) of the 92 women in the malignant group had carcinoma of the breast. Pineal calcification was present in 43 (60.6 per cent) of the 71 women with carcinoma of the breast, and in 17 (81.0 per cent) of the 21 women with other types of carcinoma. This difference is not statistically significant because of the small number in the latter group.

Thirty-six (60.0 per cent) of the 60 women with metastatic or recurrent carcinoma of the breast had calcification of the pineal body; and of the 31 of of these with metastasis to bone, 19 (61.3 per cent) had pineal calcification. The group of 11 women with carcinoma of the breast but without disseminated disease was too small for the findings to serve as a basis for conclusions concerning the effect of metastasis on the incidence of pineal calcification. However, the type of metastasis did not appear to exert any important influence.

Complete follow-ups of women with carcinoma of the breast were available in 14 having pineal calcification, and in 5 without pineal calcification. The median duration of life after onset of the disease was 4.4 years in those having pineal calcification and 2.8 years in those not having pineal calcification. The median duration of life after sex-hormone therapy was 1.5 years in nine women with pineal calcification and 3 months in three women without pineal calcification. Although definite conclusions cannot be based on findings in so few patients, those with pineal calcification appear to have a better prognosis and respond better to hormonal therapy. This possible correlation between response to therapy and pineal calcification is worthy of further investigation.

Comment

The calcific deposits in the pineal body, the so-called "brain sand granules" are laminated structures composed mainly of phosphates and carbonates of calcium and magnesium.[6] Although calcific deposition in the pineal body is believed to be the result of its degeneration,[6] there is no proof that calcification is related to hypofunction of this body. In fact, Sander and Schmid[7] noted the theory of Coronini that calcification results from crystallization of hormone. Although personal observations and also Quercy, De Lachaud, and Durand's[8] histologic study of the human pineal body suggest that calcification of this body

*$Chi\ square = 4.21;\ P < 0.05$.

may be associated with a decrease in the amount of pineal parenchyma capable of active function, the physiologic effect of such a decrease is not known.

The administration of pineal extract has been reported to inhibit the growth of experimentally induced cancer in mice,[9,10] and to cause symptomatic improvement in patients having clinical cancer.[7,11] The experimental studies concern a small number of animals, and need further confirmation; the clinical studies fail to provide adequate controls or objective evidence of improvement and include no mortality statistics.

Further inconsistencies were reported by Kitay and Altschule[1] in a review which noted that pineal injection and implantation have been consistently reported to inhibit the growth of spontaneous or induced malignant neoplasms, but that pinealectomy has been reported to accelerate the growth of sarcoma transplants in the rat as well as to inhibit the growth of spontaneous and induced cancers in mice. Thus the possible role of the pineal body in the development of carcinoma is controversial and demands further and more objective evidence.

At the present time, the explanation for the increased incidence of pineal body calcification noted in this series in women with carcinoma is not apparent. To clarify the problem, a better understanding is needed of the function of the pineal body.

Summary

In a selected series of women having carcinoma the incidence of calcification of the pineal body was significantly greater than that in a control group of women without malignant disease in the same age group. The difference in incidences of pineal calcification between men having carcinoma and those not having malignant disease was not significant.

References

1. Kitay, J. I., and Altschule, M.D.: The Pineal Gland. Cambridge, Mass.: Harvard University Press, 1954, 280 pp.

2. Simonnet, H.; Thieblot, L.; Melik, T., and Segal, V.: Nouvelles preuves de l'endocrinie epiphysaire. (New evidence of endocrine function of pineal body.) Acta endocrinol. **17**: 402-413, 1954.

3. Camp, J. D.: Intracranial calcification and its roentgenologic significance. Am. J. Roentgenol. **23**: 615-624, June 1930.

4. Mainland, D.: Elementary Medical Statistics: The Principles of Quantitative Medicine. American Monograph Series (4). Philadelphia: W. B. Saunders Co., 1952, 327 pp.

5. Frada, G., and Micale, G.: Cited by Kitay and Altschule.[1]

6. Dale, T.: Intracranial calcifications. Acta radiol. **15**: 628-634, 1934.

7. Sander, G., and Schmid, S.: Ueber die Wirkung von Epiphysenimplantationen und Epiphysenextrakten bei menschlichen malignen Tumoren. Wien. klin. Wchnschr. **64**: 505-508, July 11, 1952.

8. Quercy, P.; de Lachaud, R., and Durand, R.: Sur l'épiphyse et des formations para-épiphysaires chez l'homme adulte. Rev. neurol. **69**: 483-490, May 1938.

9. Bergmann, W., and Engel, P: Ueber den Einfluss von Zirbelextrakten auf tumoren bei weissen Mäussen und bein Menschen. Wien. klin. Wchnschr. **62**: 79-82, Feb. 3, 1950.

10. Engel, P., and Fischl, S.: Über die Wirkung von Zirbeldrüsenextrakten auf Benzopyren-tumoren. Ztschr. Vitamin-Hormon u. Fermentforsch. **6**: 259-268, 1954.

11. Altieri, A., and Sorrentino, F.: Über eine neue Hormontherapie des Prostatakrebses. Die Epiphysenextrakte Urol. internation. **2**: 312-320, 1956.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

BROWN, C. H.: New blocking agents. Am. J. Nursing **57**: 877-879, July 1957.

CARTER, F. H.; AOYAMA, SHIGETO; MERCER, R. D., and KOLFF, W. J.: Hemodialysis in children. J. Pediat. **51**: 125-136, Aug. 1957.

CRILE, GEORGE, JR.: The treatment of nodules in the thyroid. GP **16**: 78-80, July 1957.

CRILE, GEORGE, JR.: Transesophageal ligation of bleeding esophageal varices. In Current Surgical Management, edited by J. H. Mulholland, E. H. Ellison, and S. R. Friesen. Philadelphia: W. B. Saunders Co., 1957, pp. 98-99.

EFFLER, D. B.: Surgical treatment of achalasia of the esophagus and mega-esophagus. In Current Surgical Management, edited by J. H. Mulholland, E. H. Ellison, and S. R. Friesen. Philadelphia: W. B. Saunders Co., 1957, pp. 230-234.

HALE, D. E.; MORACA, P. P., and WASMUTH, C. E.: Elective cardiac arrest during cardiotomy; summary of 37 cases. Anesthesiology **18**: 378-388, May-June 1957.

HARMON, MARY C.; ZIPURSKY, ALVIN,* and LAHEY, M. E.*: Study of hemophilia. A.M.A. Am. J. Dis. Child. **93**: 375-384, April 1957.

HASERICK, J. R.: Six years' survival in severe systemic lupus erythematosus; an analysis of 12 cases. A.M.A. Arch. Dermat. & Syph. **75**: 706-714, May 1957.

HAZARD, J. B.; McCORMACK, L. J., and BELOVICH, DORIS: Exfoliative cytology of the urine with special reference to neoplasms of the urinary tract; preliminary report. J. Urol. **78**: 182-187, Aug. 1957.

HEWLETT, J. S.; McCULLAGH, E. P.; FARRELL, G. L.**; DUSTAN, HARRIET P.; POUTASSE, E. F., and PROUDFIT, W. L.: Aldosterone-producing tumors of the adrenal gland. J.A.M.A. **164**: 719-726, June 15, 1957.

HIGGINS, C. C.: Hematuria. Mississippi Valley M. J. **79**: 176-179, July 1957.

HOERR, S. O.: Management of severe upper gastrointestinal hemorrhage. Cincinnati J. Med. **38**: 253-256, July 1957.

HOERR, S. O., and HARPER, J. R.: On peripheral thrombophlebitis. J.A.M.A. **164**: 2033-2034, Aug. 31, 1957.

KOLFF, W. J.; EFFLER, D. B.; GROVES, L. K., and MORACA, P. P.: Elective cardiac arrest with potassium citrate during open-heart operations; report of thirty-seven cases. J. A. M. A. **164**: 1653-1660, Aug. 10, 1957.

LEWIS, LENA A.; OLMSTED, FREDERICK; PAGE, I. H.; LAWRY, ELEANOR Y.+; MANN, G. V.+; STARE, F. J.+; HANIG, MARTIN++; LAUFFER, M. A.++; GORDON, TAVIS†, and MOORE, F. E.†: Serum lipid levels in normal persons; findings of a cooperative study of lipoproteins and atherosclerosis. Circulation **16**: 227-245, Aug. 1957.

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†National Heart Institute, National Institutes of Health, Bethesda, Maryland.

McCUBBIN, J. W.; PAGE, I. H., and BUMPUS, F. M.: Effect of synthetic serotonin on the carotid sinus. Circulation Res. **5**: 458-460, July 1957.

McCULLAGH, E. P.: Some recent advances in endocrinology. Cincinnati J. Med. **38**: 215-225, June 1957.

McCULLAGH, E. P., and LEISER, A. E.: Turner's syndrome and Laurence-Moon-Biedl syndrome in siblings. J. Clin. Endocrinol. & Metab. **17**: 985-988, Aug. 1957.

MASSON, G. M. C.; HELMCKE, G.; CORCORAN, A. C., and PAGE, I. H.: Pressor and myotrophic activities of incubated plasma. Proc. Soc. Exper. Biol. & Med. **94**: 544-546, March 1957.

PAGE, I. H.: Arterial Hypertension, Chapter 26 in, Diagnosis and Treatment of Cardiovascular Disease, vol. 1, edited by W. D. Stroud and M. W. Stroud, III. Philadelphia: F. A. Davis Co., 1957, pp. 603-638.

PAGE, I. H.: Renal hypertension. Heart Bull. **6**: 74-76, July-Aug. 1957.

PAGE, I. H.; STARE, F. J.*; CORCORAN, A. C.; POLLACK, HERBERT,** and WILKINSON, C. F., JR.+: Atherosclerosis and the fat content of the diet. Circulation **16**: 163-178, Aug. 1957.

PHALEN, G. S., and KENDRICK, J. I.: Compression neuropathy of the median nerve in the carpal tunnel. J.A.M.A. **164**: 524-530, June 1, 1957.

POUTASSE, E. F.: Renal artery aneurysm; excision of aneurysm and repair of renal artery. J. Urol. **77**: 697-708, May 1957.

SALMOIRAGHI, G. C., and PAGE, I. H.: Effects of LSD 25, BOL 148, bufotenine, mescaline and ibogaine on the potentiation of hexobarbital hypnosis produced by serotonin and reserpine. J. Pharmacol. & Exper. Therap. **120**: 20-25, May 1957.

SKILLERN, P. G.; CRILE, GEORGE, JR.; McCULLAGH, E. P.; HAZARD, J. B.; LEWIS, LENA A., and BROWN, HELEN: Scientific exhibit: struma lymphomatosa. Postgrad. Med. **21**: 631-638, June 1957.

TUCKER, A. S.; ARAMSRI, BISAMAI, and HUGHES, C. R.: Roentgenographic diagnosis of spinal tumors. Am. J. Roentgenol. **78**: 54-65, July 1957.

TURNBULL, R. B., JR.,: Clinical recognition of postoperative micrococcic (staphylococcic) enteritis. J.A.M.A. **164**: 756-761, June 15, 1957.

WISE, R. E.; GARDNER, W. J., and HOSIER, R. B.: X-ray visualization of the intervertebral disc. New England J. Med. **257**: 6-10, July 4, 1957.

ZOLLINGER, R. M.++; GOLDBLATT, HARRY†; WARREN, K. W††.; WHEELER, W. E.,++ and ROSSMILLER, H. R.: Jaundice (symposium). Postgrad. Med. **22**: 171-182, Aug. 1957.

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***New York University College of Medicine, Bellevue Hospital, and Mt. Sinai Hospital, New York, New York.*

+*New York University Post-Graduate School of Medicine, New York, New York.*

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†*Western Reserve University School of Medicine and Mt. Sinai Hospital, Cleveland, Ohio.*

††*Lahey Clinic, Boston, Massachusetts.*

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

affiliated with

THE CLEVELAND CLINIC FOUNDATION

announces a postgraduate continuation course in hematology on October 23 and 24, 1957

Current Trends in Hematology

Tentative Program

Wednesday, October 23, 1957

Morning Session		JOHN D. BATTLE, JR., M.D., *Presiding*
8:00- 9:00	Registration	
9:00- 9:15	Introductory Remarks	CHARLES L. LEEDHAM, M.D.
9:15- 9:35	Iron-Deficiency Anemia	JAMES S. HEWLETT, M.D.
9:35- 9:55	Anemias of Infancy and Childhood	MARY C. HARMON, M.D.
9:55-10:30	Primary Refractory Anemias	LEON O. JACOBSON, M.D.*
10:30-10:50	Intermission	
		JAMES S. HEWLETT, M.D., *Presiding*
10:50-11:10	Pernicious Anemia	DONALD W. BORTZ, M.D.*
11:10-11:30	Abnormal Hemoglobin Disorders	JOHN D. BATTLE, JR., M.D.
11:30-12:15	Mechanisms in Hemolytic Diseases	CARL F. HINZ, JR., M.D.*
12:30- 2:00	Luncheon—*Courtesy of Bunts Institute*	

Afternoon Session		JOHN D. BATTLE, JR., M.D., *Presiding*
2:00- 2:20	Blood Transfusion Therapy	JOHN W. KING, M.D., PH.D.
2:20- 2:40	Hematologic Changes in Systemic Lupus Erythematosus	JOHN R. HASERICK, M.D.
2:40- 3:00	Myeloid Metaplasia	WILLIAM A. HAWK, M.D.
3:00- 3:20	Polycythemia	JAMES S. HEWLETT, M.D.
3:20- 3:40	Intermission	
		JAMES S. HEWLETT, M.D, *Presiding*
3:40- 4:30	Erythropoietin: Clinical and Theoretical Applications	LEON O. JACOBSON, M.D.*
4:30- 5:00	Panel Discussion: Investigation of Anemia of Obscure Causes	
	Moderator—RAY A. VAN OMMEN, M.D.	
	JAMES S. HEWLETT, M.D.	
	HAROLD R. ROSSMILLER, M.D.	
	JOHN D. BATTLE, JR., M.D.	

**Guest speaker.*

Thursday, October 24, 1957

Morning Session . . . . . JOHN D. BATTLE, JR., M.D., *Presiding*

9:00- 9:15 . Anemias Due to Endocrine Dysfunction . . . . PENN G. SKILLERN, M.D.

9:15- 9:40 . Idiopathic Thrombocytopenia . . . . . CLAUDE-STARR WRIGHT, M.D.*

9:40-10:00 . Hemophilia and Hemophilia-like Disorders . . JAMES S. HEWLETT, M.D.

10:00-10:20 . Malignant Lymphoma . . . . . JOHN B. HAZARD, M.D.

10:20-10:40 . Intermission

. . . . . JAMES S. HEWLETT, M.D., *Presiding*

10:40-11:00 . Pathologic Physiology of Myeloma . . . . . JOHN D. BATTLE, JR., M.D.

11:00-11:20 . Indications for Splenectomy (1957) . . . CLAUDE-STARR WRIGHT, M.D.*

11:20-12:00 . Chemotherapy of Leukemia . . . . . AUSTIN S. WEISBERGER, M.D.*

12:00-12:30 . Question-and-Answer Panel

Affiliations of Guest Speakers

DONALD W. BORTZ, M.D., Director, Division of Medicine, Westmoreland Hospital, Greensburg, Pennsylvania.

CARL F. HINZ, JR., M.D., Instructor in Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

LEON O. JACOBSON, M.D., Professor of Medicine and Director of Argonne Cancer Research Hospital, The University of Chicago, The School of Medicine, Chicago, Illinois.

AUSTIN S. WEISBERGER, M.D., Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

CLAUDE-STARR WRIGHT, M.D., Associate Professor of Medicine, Medical College of Georgia, Augusta, Georgia.

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*Guest speaker.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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THE CLEVELAND CLINIC FOUNDATION

announces a symposium on clinical chemistry methods
on November 13, 14, and 15, 1957,
sponsored by American Association of Clinical Chemists (Cleveland Section)

Tentative Program

Wednesday, November 13, 1957

Liver Function

Morning Session . . . . . ADRIAN HAINLINE, JR., PH.D., *Presiding*

8:00- 8:55	.	Registration
8:55- 9:10	.	Introductory Remarks . . . . . CHARLES L. LEEDHAM, M.D.
9:10-10:00	.	Chemical Disturbances Associated with Liver Disease . . . . . JOHN G. REINHOLD, PH.D.*
10:00-10:15	.	Intermission
10:15-10:45	.	The Clinical Significance in Alterations in Serum Transaminase . . . . . FELIX WROBLEWSKI, M.D.*
10:45-11:30	.	Factors Which Influence the Turbidity and Flocculation Tests . . . . . JOHN G. REINHOLD, PH.D.*
11:30-12:00	.	Panel Discussion

Moderator—JOHN G. REINHOLD, PH.D.*
ADRIAN HAINLINE, JR., PH.D.
FELIX WROBLEWSKI, M.D.*

12:00- 1:00	.	Luncheon
1:00- 2:00	.	Tour of the Clinical Laboratories of The Cleveland Clinic Foundation

Afternoon Session . . . . . ROGER W. MARSTERS, PH.D.,* *Presiding*

2:00- 2:45	.	Procedures and Pitfalls in Porphyrin Analysis . SAMUEL SCHWARTZ, M.D.*
2:45- 3:05	.	The Quantitative Measurement of Bile Pigment . . . . . J. WAIDE PRICE, PH.D.*
3:05- 3:20	.	Electrophoresis of Bile . . . . . MIRIAM REINER, PH.D.*
3:20- 3:35	.	Intermission
3:35- 3:50	.	The Determination of Tissue Glycogen . . ADRIAN HAINLINE, JR., PH.D.
3:50- 4:30	.	The Application of Chemical Measurements to the Study of the Liver and Biliary Tract . . . . . JOHN G. REINHOLD, PH.D.*
4:30- 5:00	.	Panel Discussion

Moderator—JOHN G. REINHOLD, PH.D.*
ADRIAN HAINLINE, JR., PH.D.
MIRIAM REINER, PH.D.*
J. WAIDE PRICE, PH.D.*
SAMUEL SCHWARTZ, M.D.*

**Guest speaker.*

Evening Session (Bunts Auditorium)

7:30- 8:30 . Horizons in Porphyrin Research . . . . . SAMUEL SCHWARTZ, M.D.*

8:45 . *Mixer* (Fenway Hall Hotel, 1986 East 107 Street)

Thursday, November 14, 1957

Electrophoresis

Morning Session . . . . . LENA A. LEWIS, PH.D., *Presiding*

9:00- 9:10 . Introductory Remarks . . . . . LENA A. LEWIS, PH.D.

9:10-10:00 . Application of Electrophoresis in the Clinical Laboratory . . . . . MIRIAM REINER, PH.D.*

10:00-10:30 . Practical Aspects of Paper Electrophoresis . . . . . WILLARD R. FAULKNER, PH.D.

10:30-10:45 . Intermission

10:45-11:15 . Determination of Total Protein . . . . . JOHN G. REINHOLD, PH.D.*

11:15-11:30 . Normal Values in Electrophoresis . . . . . LENA A. LEWIS, PH.D.

11:30-12:00 . Panel Discussion

Moderator—LENA A. LEWIS, PH.D.
WILLARD R. FAULKNER, PH.D.
MIRIAM REINER, PH.D.*
JOHN G. REINHOLD, PH.D.*

12:00- 1:15 . Luncheon

1:15- 2:00 . Tour of the Electrophoresis and Ultracentrifuge Laboratories of the Division of Research of The Cleveland Clinic Foundation

Afternoon Session . . . . . MIRIAM REINER, PH.D.,* *Presiding*

2:00- 2:45 . Electrophoretic Analysis of Fluids Other Than Serum . . . . . LENA A. LEWIS, PH.D.

2:45- 3:30 . Application of Electrophoresis to Miscellaneous Media . . . . . MIRIAM REINER, PH.D.*

3:30- 3:45 . Intermission

3:45- 4:30 . Electrophoretic Determination of Hemoglobin . . LENA A. LEWIS, PH.D.

4:30- 5:00 . Panel Discussion

MIRIAM REINER, PH.D.*
LENA A. LEWIS, PH.D.

Friday, November 15, 1957

Microchemistry

Morning Session . . . . . ADRIAN HAINLINE, JR., PH.D., *Presiding*

9:00- 9:50 . Basic Principles of Micro Techniques As Applied to the Clinical Laboratory and Their Application to Diagnosis . . . . . SAMUEL NATELSON, PH.D.*

*Guest speaker.

9:50-10:15 . Experiences in the Development of Micro Techniques ..... WILLARD R. FAULKNER, PH.D.

10:15-10:30 . Intermission

10:30-10:45 . Microdiffusion ..... WILLARD R. FAULKNER, PH.D.

10:45-10:55 . Diffusion Techniques Applied to Toxicology ... IRVING SUNSHINE, PH.D.*

10:55-11:30 . Micro Techniques and Their Application to Fluid and Electrolyte Balance ..... SAMUEL NATELSON, PH.D.*

11:30-12:00 . Panel Discussion

Moderator—SAMUEL NATELSON, PH.D.*
WILLARD R. FAULKNER, PH.D.
ADRIAN HAINLINE, JR., PH.D.
IRVING SUNSHINE, PH.D.*

12:00- 1:15 . Luncheon

1:15- 2:00 . Tour of Microchemistry Laboratory, Cleveland Clinic Hospital

Determination of Enzymatic Activity

Afternoon Session . . . . . J. WAIDE PRICE, PH.D.,* *Presiding*

2:00- 2:50 . Basic Factors in Measurements of Enzyme Activities . . . . . FELIX WROBLEWSKI, M.D.*

2:50- 3:20 . The Amylase Determination . . . . . ROGER W. MARSTERS, PH.D.*

3:20- 3:35 . Intermission

3:35- 4:05 . The Determination of Phosphatase . . . . . JOHN W. KING, M.D., PH.D.

4:05- 4:30 . The Clinical Significance of Alteration of Lactic Acid Dehydrogenase Activity in Body Fluids . . . . . FELIX WROBLEWSKI, M.D.*

4:30- 5:00 . Panel Discussion

Moderator—FELIX WROBLEWSKI, M.D.*
JOHN W. KING, M.D., PH.D.
ROGER W. MARSTERS, PH.D.*
J. WAIDE PRICE, PH.D.*

Affiliations of Guest Speakers

ROGER W. MARSTERS, PH.D., Clinical Chemist, Cleveland City Hospital, Cleveland, Ohio.

SAMUEL NATELSON, PH.D., Clinical Chemist, Department of Biochemistry, St. Vincent's Hospital, New York, New York.

J. WAIDE PRICE, PH.D., Associate Professor of Clinical Biochemistry, Department of Pathology, Western Reserve University School of Medicine, and Biochemist, University Hospitals, Cleveland, Ohio.

MIRIAM REINER, PH.D., Clinical Chemist, District of Columbia General Hospital, Washington, D. C.

JOHN G. REINHOLD, PH.D., Clinical Chemist, Pepper Laboratory of Clinical Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

SAMUEL SCHWARTZ, M.D., Associate Professor of Experimental Medicine, Department of Medicine, The Medical School, University of Minnesota, Minneapolis, Minnesota.

IRVING SUNSHINE, PH.D., Toxicologist, Cuyahoga County Coroner's Office, Cleveland, Ohio.

FELIX WROBLEWSKI, M.D., Assistant Attending Physician, Memorial Center for Cancer and Allied Diseases, and Assistant Professor of Clinical Medicine, Cornell University, College of Medicine, New York, New York.

**Guest speaker.*

REGISTRATION FORM

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Please register me for the symposium on Clinical Chemistry Methods to be held on November 13, 14, and 15, 1957. (*Registration fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.*)

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THE CLEVELAND CLINIC FOUNDATION

announces a course

Physics of Radiology

conducted by Otto Glasser, PH.D.,
on Thursday afternoons at five o'clock beginning December 5, 1957,
and lasting through April 3, 1958

Lectures will be presented by members of the faculty of The Frank E. Bunts Educational Institute in the Bunts Seminar Room, 471, North Clinic Building, 2020 East 93 Street, Cleveland, Ohio. The textbook for the course will be *Physical Foundations of Radiology*, ed. 2, 1952, by Otto Glasser, Edith H. Quimby, Lauriston S. Taylor, and J. L. Weatherwax, published by Paul B. Hoeber, Inc., 49 East 33 Street, New York 16, N. Y. It is suggested that each registrant obtain this book.

Tuition for the course is $30.00 payable in advance. To reserve a place in the course, a check for the tuition should be mailed to the Registrar, The Frank E. Bunts Educational Institute, Cleveland Clinic, 2020 East 93 Street, Cleveland 6, Ohio. Please make check payable to The Frank E. Bunts Educational Institute.

*Tentative Program**

December 5, 1957	Milestones in Radiology (Chapter I)	OTTO GLASSER, PH.D.
December 12, 1957	Fundamental Concepts of Matter (Chapter II)	OTTO GLASSER, PH.D.
December 19, 1957	Fundamental Concepts of Radiation (Chapter III)	OTTO GLASSER, PH.D.
January 2, 1958	Interaction of Radiation and Matter (Chapter IV)	OTTO GLASSER, PH.D.
January 9, 1958	Fundamental Concepts of Electricity and Magnetism (Chapter V) Production and Nature of Roentgen Rays (Chapter VI)	OTTO GLASSER, PH.D.

*Chapter numbers are those from the textbook *Physical Foundations of Radiology*.

January 16, 1958	.	Roentgen-Ray Tubes (Chapter VII) Roentgen-Ray Circuits (Chapter VIII) Supervoltage Generators, High Energy Accelerators, Nuclear Reactors (Chapter IX) . . . . . OTTO GLASSER, PH.D.
January 23, 1958	.	Physical Principles of Roentgen-Ray Diagnostic Procedures (Chapter X) . . . WILLIAM C. STRITTMATTER, M.D.
January 30, 1958	.	Measurement of Roentgen-Ray Quantity (Chapter XI) . . . . . OTTO GLASSER, PH.D.
February 6, 1958	.	Measurement of Roentgen-Ray Quality (Chapter XII) . . . . . OTTO GLASSER, PH.D.
February 13, 1958	.	Tissue Dosage in Roentgen-Ray Therapy (Chapter XIII) . . . . . THOMAS F. MEANEY, M.D.
February 20, 1958	.	Radioactivity (Chapter XIV) Measurement of Gamma-Ray Quantity (Chapter XV) . . . . . OTTO GLASSER, PH.D.
February 27, 1958	.	Dosage Calculations in Radium Therapy: A. External Gamma-Ray Therapy (Chapter XVI) . . . . . ROBERT A. HAYS, M.D.
March 6, 1958	.	Dosage Calculations in Radium Therapy: B. Intracavitary and Interstitial Therapy (Chapter XVI) . . . . . ROBERT A. HAYS, M.D.
March 13, 1958	.	Measurement of Radiation from Radioactive Isotopes (Chapter XVII) Dosage Considerations in the Use of Radioactive Isotopes (Chapter XVIII) . . . . . OTTO GLASSER, PH.D.
March 20, 1958	.	Clinical Uses of Radioactive Isotopes . JOHN D. BATTLE, JR., M.D. PENN G. SKILLERN, M.D.
March 27, 1958	.	Dependence of the Biologic Reaction of Ionizing Radiations on Quality and Time Factors (Chapter XIX) . . . . . OTTO GLASSER, PH.D.
April 3, 1958	.	Protection in Radiology (Chapter XX) . . . . . OTTO GLASSER, PH.D.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

affiliated with

THE CLEVELAND CLINIC FOUNDATION

announces a postgraduate continuation course in ophthalmology
on December 11 and 12, 1957

Tentative Program

Wednesday, December 11, 1957

Morning Session

8:15- 8:55	.	Registration
8:55- 9:00	.	Welcome . . . . . CHARLES L. LEEDHAM, M.D.
9:00- 9:30	.	Uveitis . . . . . ROSCOE J. KENNEDY, M.D.
9:30-10:30	.	Cataract Surgery Complications . . . . . A. D. RUEDEMANN, SR., M.D.*
10:30-10:50	.	Intermission
10:50-11:15	.	Current Therapy in Tuberculosis . . . . . H. S. VAN ORDSTRAND, M.D.
11:15-11:35	.	Ocular Findings Associated with Chiasmal Lesions . . . . . JAMES E. NOUSEK, JR., M.D.
11:35-12:00	.	Seminar on Treatment of Ptosis *Moderator*—ROSCOE J. KENNEDY, M.D. A. D. RUEDEMANN, SR., M.D.* BRENDAN D. LEAHEY, M.D.* JAMES S. SHIPMAN, M.D.*
12:00-12:30	.	Questions and Answers
12:30- 1:30	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session

2:00- 2:20	.	Endotracheal Anesthesia in Eye Surgery . . . . DONALD E. HALE, M.D.
2:20- 3:05	.	Choice of Operation in Wide Angle Glaucoma . . . . . JAMES S. SHIPMAN, M.D.*
3:05- 3:30	.	Indications for Oblique Muscle Surgery . . . WEBB CHAMBERLAIN, M.D.*
3:30- 3:50	.	Intermission
3:50- 4:35	.	Corneal Complications of Beta Radiation . . BRENDAN D. LEAHEY, M.D.*
4:35- 5:00	.	Questions and Answers

**Guest speaker.*

Thursday, December 12, 1957

Morning Session

9:00- 9:20	.	Migraine—Diagnosis and Treatment . . . . LEONARD L. LOVSHIN, M.D.
9:20-10:05	.	Corneal Transplantation—Observations . . . BRENDAN D. LEAHEY, M.D.*
10:05-10:30	.	Graves' Disease . . . . . E. PERRY MCCULLAGH, M.D.
10:30-10:50	.	Intermission
10:50-11:20	.	Ocular Findings in Hypertension . . . . . GEORGE LOCKHART, III, M.D.
11:20-11:50	.	Treatment of Arteriovenous Aneurysm in Pulsating Exophthalmos . . . . . W. JAMES GARDNER, M.D.
11:50-12:15	.	Questions and Answers
12:15- 1:15	.	Luncheon—*Courtesy of Bunts Institute*
1:15- 2:00	.	Tour of the Cleveland Clinic Hospital

Afternoon Session

2:00- 2:45	.	Surgical and Medical Management of Esotropia and Exotropia . . . . . A. D. RUEDEMANN, SR., M.D.*
2:45- 3:05	.	Corneal and Conjunctival Lesions . . . . . JOHN B. HAZARD, M.D.
3:05- 3:30	.	Treatment of Corneal Dystrophy . . . . . LORAND V. JOHNSON, M.D.*
3:30- 3:50	.	Intermission
3:50- 4:40	.	Retinal Detachment Surgery—Choice of Operative Procedure . . . . . JAMES S. SHIPMAN, M.D.*
4:40- 5:00	.	Questions and Answers

Affiliations of Guest Speakers

WEBB CHAMBERLAIN, M.D., Assistant Clinical Professor of Ophthalmology, Western Reserve University School of Medicine, Cleveland, Ohio.

LORAND V. JOHNSON, M.D., Professor of Ophthalmology, Western Reserve University School of Medicine, Cleveland, Ohio.

BRENDAN D. LEAHEY, M.D., Instructor in Ophthalmology, Harvard Medical School, Boston, Massachusetts.

A. D. RUEDEMANN, SR., M.D., Head of Department and Professor of Ophthalmology, Wayne University College of Medicine, Detroit, Michigan.

JAMES S. SHIPMAN, M.D., Clinical Professor of Ophthalmic Surgery, Graduate School University of Pennsylvania; Associate Professor of Ophthalmology, Jefferson Medical College of Philadelphia, Pennsylvania; Attending Surgeon, Wells Eye Hospital, Philadelphia, Pennsylvania.

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*Guest speaker.

REGISTRATION FORM

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Please register me for the postgraduate continuation course in *Ophthalmology*, to be given December 11 and 12, 1957. (*Registration fee is $20.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.*)

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